Chapter 14

Hematopoietic and Hemolymphatic Disorders

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I. ANEMIA. Although anemia literally means "no blood," medically it refers to a state of inadequate oxygen transport by circulating hemoglobin. Anemia is rarely a primary disease and is usually a secondary problem related to trauma, infection, toxicosis, or another disease process.

A. Clinical evaluation of anemia

1. Clinical findings
   a. History. A complete history of the affected animal should be taken, including:
      (1) Anthelmintic and acaricidal treatments and risk factors for infestation
      (2) Drug treatments or exposure to toxins
      (3) Dietary history (e.g., exposure to toxic plants and minerals)
      (4) Frequency of erythrocyte parasites in the region
      (5) Hemorrhage or other illnesses
   b. Clinical **signs** generally include weakness, lethargy, exercise intolerance, pallor of mucous membranes, and a loss of prominence of retinal or scleral vessels.
      (1) Chronic anemia. Poor growth and peripheral and ventral edema may be seen with chronic anemia, particularly if there is concurrent protein loss.
      (2) Severe anemia. Exertion can lead to tachycardia and tachypnea with severe anemia. If anemia is accompanied by a decrease in blood volume, tachycardia and poor jugular filling are common.
   c. Physical examination. The following should be noted during the physical examination:
      (1) Degree or presence of pallor
      (2) Degree or presence of **icterus.** (It must be noted, however, that icterus can develop in the absence of hemolytic anemia—anoretic horses frequently develop icterus due to alterations in bilirubin metabolism, and animals with liver disease also may develop icterus without hemolytic anemia.)
      (3) Urine discoloration. Red urine can be caused by hematuria, hemoglobinuria, or myoglobinuria. Dark urine can result from these factors, as well as from a high bilirubin or methemoglobin content.
      (4) Fever. Often, animals with immune-mediated hemolysis and infectious conditions present with a fever. The absence of fever does not exclude these conditions.
      (5) Signs of internal or external blood loss (e.g., epistaxis, melena, hematuria, hematochezia)
2. Classification of anemia. Anemia can be classified by mechanism, regenerative response, red cell indices, and morphology.
   a. Mechanisms. There are four causes of anemia:
      (1) Egress of red blood cells (RBCs) from the vasculature (i.e., hemorrhage) can occur due to internal or external bleeding or parasitic ingestion. **Peracute** blood loss results in a loss of **intravascular** volume and possibly **hypovolemic shock.**
      (2) **Destruction** of RBCs (hemolysis)
         (a) Intravascular hemolysis occurs when damaged erythrocytes are lysed in the blood stream.
            (i) Intravascular hemolysis can occur with some infections and toxins, osmotic damage, or with immunoglobulin M (IgM)-mediated hemolysis.
            (ii) Free hemoglobin is released into the blood, resulting in **hemoglobinemia** and hemoglobinuria (red urine).

(iii) Some hemoglobin is metabolized to bilirubin, causing icterus and dark urine.
(iv) Free hemoglobin can lead to secondary renal tubular necrosis.
(b) Extravascular hemolysis occurs when damaged erythrocytes are removed by the reticuloendothelial organs.
(i) Oxidative damage to hemoglobin, membrane changes due to drugs or infectious agents, and antibody binding (IgG) to the erythrocyte membrane are the most common causes of extravascular hemolysis.
(ii) Hemoglobin is metabolized by the reticuloendothelial cells to bilirubin and is not released into the peripheral blood.
(iii) Hyperbilirubinemia leads to jaundice and dark urine.
(3) Impaired production of RBCs can result from the suppression of bone marrow activity or the replacement of hematopoietic stem cells. Examination of bone marrow cells should reveal:
(a) A lack of hyperplasia of the precursor cells of the erythroid line
(b) Possibly a lack of megakaryocytes and myeloid precursor cells
(4) Impaired oxygen-carrying capacity of RBCs is extremely rare in large animals, but it is seen in cows with erythropoietic porphyria.
b. Regenerative response. The body's reaction to anemia is to increase erythrocyte production and release by the erythroid stem cells in the marrow. The direct stimulus for increasing erythrocyte production is erythropoietin, which is released into the blood by renal tubular cells in response to hypoxemia.
(1) Anemia can be classified as regenerative or nonregenerative, depending on the effectiveness of the marrow response.
(a) All anemias are initially nonregenerative, because it takes several days for marrow hyperplasia to occur.
(b) A strong regenerative response is more common after acute blood loss or in the presence of hemolytic anemia. A regenerative response is less likely when the anemia is caused by impaired production or chronic disease.
(2) Evidence of a regenerative response varies among large animal species.
(a) Ruminants and pigs can release large numbers of reticulocytes (i.e., large, immature erythrocytes) and other immature erythrocytes into the peripheral blood.
(i) Immature erythrocytes are larger than mature cells, resulting in **anisocytosis** and **macrocytosis,** and contain less hemoglobin per unit volume, resulting in **hypochromasia.**
(ii) The reticulocytes often contain DNA or RNA remnants, which are visible after staining as polychromasia (**basophilic** stippling).
(iii) The reticulocyte count adjusted for anemia can be used to test the effectiveness of the regenerative response. The adjusted reticulocyte count is calculated and interpreted as shown in Table 14-1.
(b) All large animal species should develop hyperplasia of erythroid precursor cells in the bone marrow. Lack of this reaction is strong evidence of a nonregenerative anemia.
(c) An increase in erythrocyte count over time is the best evidence that regeneration is occurring.

TABLE 14-1. Calculating the Adjusted Reticulocyte Count

$$\frac{\text{Reticulocyte count}}{\text{Total erythrocyte count}} \times \frac{\text{PCV}}{\text{Mean PCV for species}} \times 100$$

A value of 2.0 or greater indicates a regenerative response.
A value of 0.5 or less indicates a nonregenerative response.
A value of 0.5–2.0 indicates an early or impaired response.

PCV = packed cell volume.

TABLE 14-2. Calculation of Red Cell Indices

$$\text{MCV (fL)} = \frac{\text{PCV} \times 10}{\text{Erythrocyte count (millions)}}$$

$$\text{MCH (pg)} = \frac{\text{Blood hemoglobin concentration (g)} \times 10}{\text{Erythrocyte count (millions)}}$$

$$\text{MCHC (g/dL)} = \frac{\text{Blood hemoglobin concentration (g/dL)} \times 100}{\text{PCV}}$$

MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular wlume; PCV = packed cell volume.

c. Red cell indices. Calculation of the mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) aids in the classification of anemia (**Table 14-2**).
(1) MCV. The MCV of small ruminants is typically half that of cattle or horses. Normocytic, **microcytic,** and **macrocytic** refer to normal, low, and high MCV, respectively.
(a) **Microcytosis** occurs with iron deficiency and some immune-mediated hemolytic anemias.
(b) Macrocytosis occurs with maturation defects (e.g., cobalt or vitamin B_{12}/folate deficiency, some systemic diseases) or the release of immature erythrocytes into the peripheral blood, which is a normal regenerative response to anemia (particularly anemia due to acute blood loss or hemolysis).
(2) MCH decreases with most causes of anemia as a result of decreased erythrocyte count. MCH may increase **artifactually** with intravascular hemolysis because free hemoglobin in the blood is also measured.
(3) MCHC. Normochromic, hypochromic, and hyperchromic refer to normal, low, and high MCHC, respectively.
(a) Normochromasia is common with nonregenerative anemia.
(b) Hypochromasia can accompany microcytosis (and low MCH) with iron deficiency or macrocytosis (with a normal to high MCH) with the release of immature erythrocytes into the blood as part of a regenerative response.
(c) **Hyperchromasia** can occur with intravascular hemolysis due to the measurement of free hemoglobin in the blood.
d. Morphology. Microscopic examination of a blood smear can be used to describe the size, shape, and staining characteristics of erythrocytes.
(1) **Reticulocytosis** occurs when reticulocytes are released into the blood as part of the regenerative response to anemia. Reticulocytosis is seen only in ruminants and pigs, never in horses.
(2) **Anisocytosis** refers to cells of varying sizes in peripheral blood. Mild anisocytosis is common in ruminants, but marked **anisocytosis** (due to macrocytosis and reticulocytosis) is usually a sign of a regenerative response. Anisocytosis may also be seen after a transfusion if the host and donor erythrocytes are different sizes.
(3) Basophilic stippling (granulation) in erythrocytes stained with Romanowsky stain is the result of DNA remnants. This stippling is seen as part of the regenerative response in cattle and with chronic lead toxicosis. Howell-Jolly bodies are similar dark-staining nuclear remnants that are normally seen in horse erythrocytes and, thus, are of little value in determining regenerative response.
(4) **Spherocytosis** refers to small erythrocytes that lack central pallor. Spherocytosis usually results from partial removal of the red cell membrane by reticuloendothelial cells and often accompanies extravascular hemolysis. Spherocytes

are difficult to identify in large animals because of the small size of normal erythrocytes.

(5) Heinz bodies are aggregates of hemoglobin that have undergone oxidative denaturation. Heinz bodies are visible as refractile bodies when stained with Romanowsky stain or as round, darkly staining peripheral bodies within erythrocytes when stained with new methylene blue stain.

(6) Methemoglobin is formed when the ferrous (2^+) iron of hemoglobin is oxidized to its ferric (3^+) form. A small amount of methemoglobin is present normally and more is formed in some animals with oxidative injury (often in conjunction with Heinz body anemia). Methemoglobinemia and methemoglobinuria cause brown discoloration of the blood and urine, respectively.

(7) Erythrocyte aggregation can result from rouleaux formation or autoagglutination.

(a) Rouleaux are normal in horses and dissipate when diluted with saline.

(b) Autoagglutination is seen during inflammatory reactions and when erythrocytes are coated with antibody. Autoagglutinating erythrocytes do not disperse as readily with saline dilution.

3. Diagnostic plan and laboratory tests

a. Blood work

(1) Complete blood cell count (CBC) and morphologic examination. Anemia can be quantified by measuring the:

(a) Packed cell volume (PCV). The PCV, the percentage of blood volume occupied by erythrocytes, can be determined by automated counter or centrifugation. Microcentrifugation may be necessary to adequately pack small ruminant erythrocytes.

(b) Blood hemoglobin concentration

(c) Blood erythrocyte count

(d) **Microcytic** hypochromic anemia is suggestive of iron deficiency, whereas **macrocytic** hypochromic anemia is suggestive of a regenerative response (seen with acute blood loss or hemolysis). Normocytic normochromic anemia is seen before the regenerative response has started (2–4 days) or with nonregenerative anemia.

(e) Anemia with hypoproteinemia is suggestive of acute blood loss, whereas anemia with hyperproteinemia is suggestive of an inflammatory reaction.

(f) Agglutination may be seen. If not, a Coombs' test may be performed to test for antibody binding.

(g) Erythrocytes should be examined for morphologic abnormalities, regenerative response, or parasites.

(h) Yellow plasma is seen with hyperbilirubinemia, whereas pink plasma is seen with hemoglobinemia. Whole blood may be dark brown with severe methemoglobinemia.

(2) **Direct** Coombs' test. Specific anti-immunoglobulin and anticomplement antibodies may be mixed with host erythrocytes. If host erythrocytes are coated with these factors, as often occurs with immune-mediated hemolysis, agglutination may occur. The test is usually performed at body temperature (warm agglutination) for IgG and below body temperature (cold agglutination) for IgM. A Coombs' test cannot be performed on blood that autoagglutinates.

(3) Iron-binding capacity. Serum iron concentration and unbound iron-binding capacity can be measured. Both are low with anemia of chronic disease, whereas unbound iron-binding capacity is high with iron deficiency anemia.

b. Fecal **occult** blood test detects the presence of blood peroxidase in feces and, therefore, helps identify gastrointestinal hemorrhage. Dietary factors in ruminants and small subclinical ulcerations affect the diagnostic value of this test. The sensitivity and specificity of this test has not been established for large animals. However, test results can be used to raise or lower clinical suspicion of gastrointestinal bleeding.

c. Urinalysis

(1) Urine sediment should be examined for erythrocytes. If hematuria is present, urinary tract hemorrhage may be the source of blood loss.

(2) Tests may be performed to differentiate hemoglobin from **myoglobin** in red urine. Hemoglobinuria is seen with hematuria or intravascular hemolysis.

(3) A high urine bilirubin concentration may be seen with hemolysis or liver dysfunction (or fasting in horses).

d. Bone marrow examination can be performed in order to examine the stem cell response to anemia. Because horses do not get reticulocytosis, cytologic examination of marrow is the best way to determine if anemia is regenerative. Hyperplasia of stem cell lines, particularly erythroid precursor cells, suggests a regenerative response.

B. Acute blood loss anemia

1. Clinical findings. Animals with rapid external blood loss may have obvious hemorrhage or ectoparasitism. With internal hemorrhage, the site of hemorrhage may not be obvious.

a. Signs of anemia include pale pink to white mucous membranes, disappearance of visible **scleral** vessels, and prolonged capillary refill times.

b. Animals with blood loss anemia also often have tachycardia, weak pulses, poor jugular filling, and cold extremities.

c. Animals with poor organ perfusion become weak and dull.

2. Etiology and pathogenesis

a. Etiology. Rapid loss of blood from the vascular compartment can occur internally or externally. Blood loss can be caused by the rupture of a large, blood-filled viscus (e.g., vessel, spleen, heart), thrombocytopenia, a cloning factor defect, blood-sucking parasites, or severe ulceration of an epithelial membrane.

b. Pathogenesis. Decreased intravascular volume and hemoglobin content result in low cardiac output and poor tissue perfusion. Severely affected animals develop hypovolemic shock and may die.

3. Diagnostic plan and laboratory tests

a. Clinical findings support a diagnosis of blood loss anemia, particularly when external hemorrhage is present.

b. Blood work

(1) With **peracute** blood loss, blood appean normal and has a normal PCV, total protein, and hemoglobin concentration.

(2) With acute, subacute, or chronic blood loss anemia, blood appears thin and watery and has a low PCV, total protein, and hemoglobin concentration.

(3) After a few days of blood loss, there should be evidence of a regenerative response.

4. Therapeutic plan. Treatment is dictated by the degree, rapidity, and severity of blood loss. Efforts should be made to correct the cause of blood loss. Less aggressive intervention is required with gradual blood loss because of the animal's ability to compensate.

a. Fresh whole blood is the best treatment

b. Isotonic or hypertonic fluids should be given intravenously to restore vascular volume in patients with hypovolemic shock.

c. Stress to the animal should be minimized.

C. Chronic blood loss anemia

1. Clinical findings

a. Affected animals typically appear unthrifty, with **poor** body **condition** and hair coats. Pallor of mucous membranes may be present, but often is not remarkable.

b. Animals with longstanding concurrent hypoproteinemia often develop edema of the ventrum and extremities.

c. Severely affected animals are weak and lethargic and may die if stressed.

2. Etiology. Chronic blood loss can be caused by all of the causes of acute blood loss (see I B *2)*. Parasitism and gastrointestinal **mucosal** ulceration are the two most common causes in large animals. Because of the animal's ability to maintain circulatory

volume with chronic blood loss, hypovolemic shock is not seen. Clinical signs result from the decreased oxygen-carrying capacity of blood.

3. Diagnostic plan and **laboratory** tests
   a. Blood work. Determination of the PCV and hemoglobin concentration are necessary to diagnose chronic blood loss anemia. The regenerative response often is absent or poor, and there is occasionally hypochrornasia and microcytosis compatible with iron deficiency.
   b. Identifying the cause of blood loss through fecal examination for endoparasites, visual inspection for ectoparasites, and endoscopic examination for gastric ulceration may be useful.

4. Therapeutic plan. Specific treatment for chronic blood loss anemia usually is not indicated. Iron supplements may be helpful. Efforts should focus on treating the cause of blood loss.

D. **Hemolytic** anemia (HA)

1. HA of horses
   a. Infectious causes of HA
      (1) Babesiosis **(piroplasmosis)**
         (a) Clinical findings. Fever and icterus are common findings with both causative organisms, whereas hemoglobinuria is more common with Babesia *equi* than with Babesia caballi. Generalized signs are seen with severe anemia and include weakness, anorexia, and depression. Eyelid swelling and naso-ocular discharges are common with severe disease.
         (b) Etiology and pathogenesis
            (i) Etiology. This disease is caused by the protozoan parasites 8. caballi and B. equi. Both organisms are predominately found in tropical and subtropical areas but potentially can be found anywhere within the ranges of their host, ticks. Both organisms live within erythrocytes; 8. *equi* also has a lymphocytic stage.
            (ii) Pathogenesis. Babesia species are spread by Dermacentor, *Hyalomma,* and *Rhipicephalus* ticks. Vertical transmission in ticks occurs with B. *caballi* but not with B. equi. The parasites cause both **intra-** and extravascular hemolysis, and most infected horses remain carriers for life.
         (c) Diagnostic plan and laboratory tests. Identification of *Babesia* in a blood smear examination from a horse with compatible clinical signs is diagnostic. *B. caballi* are large and pyriform, whereas *B. equi* piroplasms are small and rounded. Multiple organisms can be found inside a single erythrocyte, occasionally forming the "Maltese cross" shape with *B.* equi. Serologic tests are also available.
         (d) Therapeutic plan. **Imidocarb** is the drug of choice to treat equine **babesiosis**. High doses are needed to treat *B.* equi and to prevent the carrier state with *B. caballi.* High doses (4 mg/kg body weight) have been associated with colic signs and death, particularly in donkeys.
         (e) Prevention. There is no vaccine for equine babesiosis. Tick control is essential to prevent the spread of the organisms.
      (2) Equine infectious anemia **(EIA;** swamp **fever)**
         (a) Patient profile. EIA only infects horses and other Equidae, regardless of age, breed, or sex. The disease is found worldwide.
         (b) Clinical findings. The clinical and hematologic manifestations vary depending on the virulence of the virus, host resistance factors, and environmental stressors. Ninety percent of acute and subacute episodes occur within the first year of infection. Recrudescence of clinical signs may occur in association with corticosteroid administration, stressors **(e.g.,** transport, heavy work), intercurrent disease, or adverse environmental factors. There are three forms of clinical disease:
            (i) Acute form. Clinical signs include intermittent fever, depression, petechial hemorrhages, progressive weakness, weight loss, anemia, swelling of the legs, brisket and ventral abdomen, or sudden death.
            (ii) Subacute to chronic form. Clinical signs include recurrent episodes of fever, depression, anemia, icterus, lymphadenopathy, petechial hemorrhages, edema, and weight loss. Occasionally, there are neurologic alterations. Clinical signs usually occur within the first few months after infection.
            (iii) Chronic or inapparent form. There may be few clinical or hematologic signs. Occasionally, carrier animals have periodic fever or weight loss.
         (c) Etiology. EIA is caused by a **lentivirus,** which is a nononcogenic retrovirus that infects cells of the immune system.
         (d) Pathogenesis. EIA virus is host-specific and is transmitted from animal to animal through body fluids, particularly blood. Infected horses are carriers for life.
            (i) Transmission. Contaminated needles, syringes, and surgical or dental instruments may spread the disease. Horse flies and deer flies can also transmit infected blood to uninfected horses. The chance of spread of EIA virus via arthropod transmission is dependent on the distance between infected and uninfected horses, the number of vector flies feeding on the horses, the amount of infected blood ingested, and other factors.
            (ii) Viral life cycle. The virus multiplies in lymphoid tissues throughout the body within monocyte and macrophage cells. The **virus** elicits brisk **humoral** and cellular immune responses. It incorporates into the host genome and is disseminated throughout the body. The virus escapes the host's **immunosurveillance** by remaining intracellular and by altering its surface glycoproteins to appear unrecognizable m surface neutralizing antibodies.
            (iii) Clinical manifestations. Many of the clinical manifestations of EIA infection are thought to be immune-mediated. Hepatitis, **lymphadenopathy**, and splenomegaly are caused by infiltrates of virus-infected mononuclear cells. Anemia results from the negative effects of the virus on hematopoiesis, viral hemagglutinin-mediated hemolysis and **phagocytosis,** and relative iron deficiency.
         (e) Diagnostic plan and laboratory tests
            (i) Clinical pathology. There may be a mild **lymphocytosis** and **monocytosis** during acute disease, but changes in the leukogram are inconsistent. **Inapparent** carriers may have a normal hemogram except for a marginally low erythrocyte count.
            (ii) Agar-gel **immunodiffusion** (ACID, **Coggins)** test is a highly specific and accurate indication of EIA infection. Test results may be negative in the first 10–14 days of disease. False-positive tests may occur in foals born to infected dams because of the absorption of antibodies from the colostrum.
            (iii) Competitive enzyme-linked **immunosorbent** assay **(ELISA)** is more sensitive but less specific than **AGID.**
         (f) Therapeutic plan. There is no effective treatment for EIA. State and federal regulations require that infected horses be reported. Only seronegative horses can be moved between states and internationally for participation in equestrian events.
         (g) Prevention. It is generally recommended (and may be required) to humanely destroy infected horses because even clinically normal chronic carrier horses pose a health risk to other horses. To avoid euthanasia, infected horses must be separated by at least *200* yards fmm healthy horses, and strict insect control must be practiced to ensure no **transmission** of disease. Strict attention to contaminated needles, syringes, or surgical instruments is also necessary.

b. Immune-mediated causes of HA
(1) Neonatal isoerythrolysis (NI)
(a) Epidemiology. In Thoroughbreds, NI occurs in approximately 1% of births. In Standardbreds, NI occurs in approximately 2% of births. The prevalence of NI is higher in mule foals (10%) because of the unique donkey erythrocyte antigen, which is present on donkey but not horse erythrocytes. Because mule foals are the product of a donkey sire and a horse dam, NI is possible in all such breedings, particularly if the dam has previously carried a mule foal.
(b) Clinical findings. The severity of clinical signs appears to relate to the amount of colostrum absorbed; therefore, vigorous foals are often the most severely affected.
(i) Foals are born healthy but develop progressive lethargy and weakness 24–36 hours postpartum after ingesting colostrum.
(ii) Mucous membranes are initially pale and later become icteric.
(iii) There may be hemoglobinuria and hemoglobinemia before death.
(iv) Other signs include rapid, shallow breathing followed by labored breathing, tachycardia, excessive yawning, and seizure-like activity.
(c) Etiology and pathogenesis. Coating of foal RBCs with maternal alloantibodies absorbed from colostrum causes RBC destruction.
(i) Blood group antigens. This condition can occur whenever the sire and foal share a blood group antigen that is not present in the mare. The Aa and Qa blood group antigens, as well as a unique donkey blood group antigen, appear to be strongly immunogenic and are responsible for most cases of NI.
(ii) Exposure in the mare. In order to have antibodies against these blood types in colostrum, the mare's blood must lack the antigen, and the mare must have been previously exposed to this antigen by blood transfusion, exposure to blood from a previous foal (usually sired by the same male) during parturition, or exposure to the foal's blood during gestation due to placental pathology.
(iii) Exposure in the foal. When antibodies are absorbed from the colostrum into the foal's circulation, they attach to the foal's erythrocytes, leading to accelerated erythrocyte removal and destruction by reticuloendothelial cells.
(d) Diagnostic plan and laboratory tests
(i) Clinical pathology reveals anemia, hemoglobinemia, elevated bilirubin (mostly conjugated), and hemoglobinuria. Mule foals may also have thrombocytopenia. The leukogram should be evaluated to help eliminate sepsis as the cause of clinical signs.
(ii) Lytic or precipitation tests detect antibodies in the colostrum or the mare's serum against the foal's whole erythrocytes. The jaundice foal agglutination (JFA) test is performed by mixing the mare's serum or colostrum with the foal's erythrocytes. Agglutination should occur with NI.
(iii) Direct Coombs' test This test also detects antibodies in the colostrum or the mare's serum against the foal's whole erythrocytes.
(e) Therapeutic plan
(i) Blood transfusion. If anemia becomes severe (i.e., when the PCV is less than 15% and decreasing over time), a whole blood transfusion should be considered. If the mare is used as the donor, all plasma must be removed by washing the mare's erythrocytes. Almost any horse's blood can be used for mule foals, but donkey blood should not be used. In general, horses that lack the Qa or Aa antigens or antibodies against them are the best donors.
(ii) Supportive care includes intravenous fluids to maintain hydration, promote diuresis of hemoglobin, and correct electrolyte and acid–base imbalances. Efforts should be made to minimize stress and restrict activity until the foal's condition is stable.

(iii) Immunosuppressive drugs are not effective against NI because the agglutinating antibody is exogenous.
(f) Prevention includes:
(i) Blood typing. Broodmares at risk for the development of NI can be identified by blood-typing. Any mare that is negative for either Aa or Qa antigen is at risk and should preferably only be bred with Aa- or Qa-negative stallions.
(ii) Serum screening. If blood typing cannot be done before breeding or if a potentially incompatible match cannot be avoided, the mare's serum should be screened for the presence of antierythrocyte antibodies within 30 days of foaling. This is done by mixing the mare's serum with the stallion's erythrocytes and looking for agglutination. This test can be repeated closer to foaling if the results are equivocal. If the blood test is positive, a JFA test should be performed before allowing the foal to nurse. If the JFA test is positive, colostrum from another source should be provided to the foal, or antibodies should be supplied by plasma transfusion from a suitable donor. When the foal can no longer absorb colostral antibody (usually by 48 hours postpartum), the foal can be allowed to nurse from the mare.
(2) Immune-mediated HA
(a) Clinical findings. Clinical signs, including fever and icterus, resemble those seen with parasitic immune-mediated hemolytic disorders (e.g., Babesiosis).
(b) Etiology and pathogenesis. Host antibodies and complement may bind to host erythrocyte membranes. This may result in intravascular hemolysis but more commonly leads to erythrocyte phagocytosis or partial phagocytosis by reticuloendothelial cells (extravascular hemolysis). This antibody binding may occur for two reasons: the alteration of the RBC membrane or an overzealous immune response. Changes in the membrane are more common and can result from:
(i) Intraerythrocyte parasites
(ii) Chronic bacterial and viral infections
(iii) Lymphosarcoma
(iv) Disorders of immune function (e.g., systemic lupus erythematosus, neonatal isoerythrolysis)
(v) Medications (particularly penicillin)
(vi) Idiopathic causes
(c) Diagnostic plan and laboratory tests. Spontaneous autoagglutination or a positive Coombs' test should be used to confirm immune-mediated hemolysis.
(d) Differential diagnoses. Parasitic diseases and EIA should be ruled out by a blood film examination or serologic tests.
(e) Therapeutic plan. All prior medications should be discontinued.
(i) Immunosuppressive drugs. If an acute or chronic infectious condition can be ruled out, an immunosuppressive course of corticosteroids or cyclophosphamide can be initiated. The dosages of these drugs should be gradually reduced, and their administration should be discontinued within 1 month, if possible.
(ii) If a noninfectious disease state (e.g., lymphosarcoma, systemic lupus erythematosus) is identified, treatment of the primary disease may result in the resolution of hemolysis.
(iii) Infectious diseases should be treated with the appropriate drugs, but classes of drugs that may have precipitated hemolysis should be avoided.
(iv) A blood transfusion is rarely necessary.
c. Toxic causes of HA
(1) Oxidative injury (red maple leaf, onion, and phenothiazine toxicosis)
(a) Patient profile. Red maple leaf toxicosis occurs in late summer and fall.

Any horse or pony is susceptible regardless of age, breed, or sex. Horses are less susceptible to onion toxicity than cattle, but they are more susceptible than sheep or goats. All horses are susceptible to phenothiazine toxicosis.

(b) Clinical findings
(i) Clinical signs. Polypnea, tachycardia, weakness, depression, anorexia, and cyanosis are common. Death may occur in 4–6 days.
(ii) Fever may be present during the hemolytic episode.
(iii) A brownish discoloration of blood and urine may occur with red maple leaf toxicosis.

(c) Etiology. Ingestion of onions or wilted, dry red maple leaves or the administration of phenothiazine sedatives or anthelmintics can lead to severe, acute hemolytic anemia.

(d) Pathogenesis. Oxidative denaturation of hemoglobin by n-propyl disulfide (an alkaloid) from onions, by an unknown toxin in red maple leaves (Acer *rubrum*), and by phenothiazines results in the production of Heinz bodies within RBCs. Red maple leaf toxicosis also causes methemoglobinemia.
(i) Onion toxicity. The alkaloid n-propyl disulfide depletes the intraerythrocytic enzyme, glucose 6-phosphate dehydrogenase, which maintains glutathione in its reduced state. When glutathione is oxidized, mixed disulfide linkages form between globin chains of hemoglobin and glutathione. These linked molecules precipitate within the cell, forming Heinz bodies.
(ii) **Phenothiazines** are also strong oxidizing agents.
(iii) Red maple leaf toxicosis. Erythrocytes containing Heinz bodies are removed from the circulation by the reticuloendothelial system (extravascular hemolysis), leading to anemia. With severe oxidative damage, some intravascular hemolysis can occur. There are two patterns of toxicity with red maple leaf toxicosis. The **peracute** form results from massive methemoglobinemia, causing marked tissue anoxia and sudden death. The hemolytic form is caused by continuous oxidative stress on RBCs, causing Heinz body anemia with subsequent intra- and extravascular hemolysis.

(e) Diagnostic plan and laboratory tests
(i) Clinical pathology. Anemia is present with all three diseases. Spherocytes, Heinz bodies in peripheral blood, and elevated total bilirubin (mostly unconjugated) may also be seen. High MCHC and MCH values support the diagnosis of intravascular hemolysis. Urinalysis may reveal elevated protein and blood and the presence of hemoglobin, bilirubin, and urobilinogen. Methemoglobinuria, **methemoglobinemia**, and low glutathione levels should be found with red maple leaf toxicosis but should not be evident with the other two diseases.
(ii) Postmortem findings include generalized icterus, petechiae and ecchymoses on serosal surfaces, and splenic engorgement. There may be a dark brown discoloration to the blood and tissues and changes in liver architecture. **Histopathologic** findings include the presence of hemoglobin, renal tubular casts and mild nephrosis, and extensive erythrophagia by macrophages.

(f) Differential diagnoses. Other causes of hemolysis or methemoglobinemia should be eliminated.

(g) Therapeutic plan
(i) Eliminate red maple leaves or onions from the diet by moving the horse. Discontinue the use of phenothiazines.
(ii) Intravenous isotonic fluids are useful for diuresis, the correction of dehydration, electrolyte depletions, and acid–base abnormalities.
(iii) Whole blood transfusion may be necessary if the PCV is less than 12% and decreasing over time.
(iv) Dexamethasone may help stabilize erythrocyte membranes and reduce the risk of a transfusion reaction. Steroids must be used with caution because they may lead to laminitis.
(v) Ascorbic acid (125 mg/kg orally initially, followed by 50 mg/kg subcutaneously twice daily) has been used as an antioxidant for the treatment of red maple leaf toxicosis.

(2) Iatrogenic causes of HA. Several medications that are commonly administered to large animals cause hemolysis. Unless large amounts of the medication are administered, hemolysis is rarely clinically significant.
(a) Hypotonic solutions can cause osmotic lysis of RBCs when administered intravenously.
(b) Phenothiazine **tranquilizers** and **anthelmintics** cause oxidative injury to RBCs [see I D 1 c (1)].
(c) Some concentrated drugs, notably tetracycline and dimethylsulfoxide (DMSO), cause hemolysis by an undescribed mechanism. To avoid this, these drugs should be diluted (less than 10% solution for DMSO) before intravenous administration.

2. HA of ruminants can also be categorized as intra- or extravascular. Each type leads to the characteristic abnormalities as discussed with horses (see I D 1).
a. Infectious causes of HA
(1) **Anaplasmosis**
(a) Clinical findings are related to the immune-mediated loss of circulating erythrocyte mass. Calves under 1 year of age show few clinical signs. Severity of clinical disease increases with age, such that cattle older than 3 years often die of peracute disease. All of the following forms can occur in infected sheep and goats, but clinical disease is rare.
(i) Acute anaplasmosis is common in young adult cattle. Anemia, fever, tachycardia, tachypnea, weakness, depression, and icterus are seen. Blood appears thin, and mucous membranes appear pale.
(ii) **Peracute** anaplasmosis is more common in older cattle. Signs are similar to the acute disease, except that death often occurs before icterus develops.
(iii) Chronic anaplasmosis can follow acute infection and is characterized by ill-thrift and decreased production. The animal becomes a reservoir for the infection of herd mates.
(b) Etiology. The disease in cattle is caused by ***Anaplasma marginale marginale*** and Anaplasma ***marginale centrale*** of the order Rickettsiales. The disease in small ruminants is caused by ***Anaplasma ovis.*** These organisms are obligate intracellular parasites of erythrocytes.
(c) Pathogenesis
(i) Transmission. The organisms are spread by the passage of blood between animals. Chronically infected animals and wild ruminants a d as reservoirs. **Argasid** and ixodid ticks, **biting** flies, and veterinary instruments are the most common means of transmission. Transmission is seasonal, based on the life cycle of the arthropod vectors. Experimental **transplacental** transmission has been documented.
(ii) Disease progression. After an incubation period of 2–7 weeks, parasitized erythrocytes begin to be removed by the reticuloendothelial system. Immune-mediated extravascular hemolysis leads to anemia.
(d) Diagnostic plan and laboratory tests. Because clinical signs are specific to hemolytic anemia but not anaplasmosis, laboratory tests can be used to confirm the diagnosis.
(i) Blood smears reveal **reticulocytosis,** polychromasia, Howell-Jolly bodies, and **basophilic** stippling. ***Anaplasma*** may be visible on direct smear as **refractile** bodies or in Giemsa-stained smears as small, round, purple bodies. A. ***marginale marginale*** are located at the periphery of erythrocytes, whereas A. marginale centrale are located toward the center.
(ii) Serologic tests and DNA probes. Chronically infected animals haw

fewer visible rickettsia and may be better diagnosed by serologic tests or DNA probes.

(e) **Therapeutic** plan. The three considerations of treatment include the resolution of acute parasitemia, maintenance of organ perfusion, and prevention of the carrier state.

(i) Oral chlortetracycline and parenteral oxytetracycline are the most commonly used drugs to treat acute or chronic infection. Low concentrations of a tetracycline (usually chlortetracycline) added to the feed or water can be used to reduce morbidity during periods of high transmission in endemic areas. Higher doses or longer treatment courses are required to eliminate infection.

(ii) Although fluids or blood transfusions can be used to maintain organ perfusion, these treatments are usually impractical.

(iii) Efforts should be made to minimize stress and exertion of severely affected cattle until parasitemia is reduced and circulating erythrocyte mass has been restored.

(f) Prevention. The control of vectors, reduction of parasitemia through the continuous use of antimicrobial drugs, elimination of the carrier state, or vaccination can be used to reduce the losses caused by anaplasmosis.

(2) **Babesiosis** (piroplasmosis) has been eradicated from North America.

(a) Patient profile. Cattle, goats, sheep, and swine may be affected.

(i) Cattle of all ages are susceptible to this disease, although calves between the ages of 2 and 9 months appear to be resistant. Offspring of exposed dams are protected against clinical disease by colostral antibody during the neonatal period. Exposed calves develop long-lasting resistance to clinical babesiosis.

(ii) *Bos* indicus cattle and their calves appear to be more resistant than other cattle.

(b) Clinical findings

(i) Clinical signs. Fwer often is present for several days before other signs appear. Anemia, depression, tachycardia, icterus, and weakness are common. Hemoglobinuria helps distinguish babesiosis from diseases characterized by extravascular hemolysis (e.g., anaplasmosis). Neurologic signs (e.g., convulsions, somnolence) are common in the hours before death.

(ii) **Necropsy** lesions. With anoxic organ damage, severe disease ensues, and death is common. Necropsy lesions include icterus and dark, swollen internal organs.

(c) Etiology. The disease is caused by protozoan parasites of the species Ba*besia. Babesia bigemina* and Babesia *bovis* are the main pathogenic species. These organisms are obligate intracellular parasites of erythrocytes.

(d) Pathogenesis

(i) Transmission between animals is by ticks. *Boophilus* species and *Ix*odes ricinus are the most important tick vectors. Transovarial transmission to the next generation of ticks plays a major role in the transmission to cattle.

(ii) After an incubation period of 2–3 weeks, the number of parasites can increase enough to become clinically relevant Intraerythrocyte parasitism leads to intravascular hemolysis with hemoglobinemia and hemoglobinuria ("redwater"). Babesia also releases toxins that cause vasodilation, increased vascular permeability, and erythrocyte aggregation. These effects on the vasculature impair circulation, leading to tissue hypoxia and necrosis. Renal damage also results from exposure to hemoglobin.

(e) Diagnostic plan and laboratory tests. Clinical signs and necropsy lesions often are adequate to diagnose babesiosis in an endemic area.

(i) **Hemogram** evaluation should reveal anemia with evidence of a regenerative response.

(ii) The parasites can be seen on **Giemsa-stained** smears and are seen as single or paired large ovoid or pyriform organisms within erythrocytes. Organisms are more readily seen on smears of peripheral blood (as opposed to jugular blood).

(iii) Serologic tests are also available.

(f) Therapeutic plan and prevention. A variety of babesiocides are available for the treatment of clinical disease. These include imidocarb, **diminazene**, phenamidine, and amicarbalide. Imidocarb and diminazene can also be used for short-term prophylaxis. Any treatment or prevention protocol should include provisions for tick control.

(3) Eperythrozoonosis. Eperythrozoon species, rickettsial parasites, are similar to Anaplasma because these organisms stimulate immune-mediated hemolysis. There are two principal species that affect ruminants and a third that affects pigs.

(a) ***Eperythrozoon wenyoni***

(i) Patient **profile.** Cows of all ages appear to be susceotible to infection by this organism.

(ii) Clinical findings. Affected cattle typically have transient fever, lymphadenopathy, depression, and decreased milk production. Swelling of the udder and hind legs is common in dairy cattle. Icterus is uncommon and mild when present.

(iii) Etiology. Although arthropod vectors are suspected, this has not been proven. Most infections appear to result in minimal clinical disease, but some cattle show clinical signs of inflammation and hemolytic anemia similar to those seen with acute anaplasmosis. Chronic infections and a subclinical carrier state are thought to occur.

(iv) Diagnostic plan and laboratory tests. Diagnosis is made by identifying the parasite on a peripheral blood smear examination. The organism is small, frequently round (but occurs in a variety of shapes), and found within erythrocytes. The organism may be seen singly, in clumps, or in a ring form. The ring form, together with a relatively large number of free organisms in blood, helps differentiate this disease from anaplasmosis.

(v) Therapeutic plan. Clinical signs usually resolve spontaneously in 7–10 days, except in immunocompromised or splenectomized cattle. More rapid resolution is seen after the administration of a single dose of a **long-acting** oxytetracycline or a 3-day course of a **short-acting oxytetracycline.**

(b) ***Eperythrozoon*** ovis

(i) Patient profile. All ages of sheep appear to be susceptible to this organism, but clinical disease is most common in young animals.

(ii) Clinical findings. Fever, depression, weakness, icterus, and hemoglobinuria are seen with severe disease. The more common manifestation is ill-thrift syndrome in lambs. Affected lambs grow poorly, have poor hair coats and pot bellies, and are easily stressed by exertion.

(iii) Etiology and pathogenesis. Other pathogens have been isolated from sheep with ill-thrift syndrome, so *E.* ovis is only one of several possible etiologic agents. Ticks, keds, and mosquitos are thought to be important vectors. Similar to *E.* wenyoni in cattle, *E. ovis* infection is thought to result in minimal clinical disease in most affected sheep. However, hemolytic anemia and the inflammatory response appear to cause morbidity and mortality in some sheep.

(iv) Diagnostic plan and laboratory tests. Similar to *E. wenyoni* infection in cattle, the diagnosis is made by identifying round or pleomorphic organisms both within plasma and erythrocytes. Clumps, crosses, and rings are a common finding.

(v) Therapeutic plan. Oxytetracyclines are probably the best drugs to treat this infection. Other drugs have been used with mixed results. In some cases, treatment failure may result from failure to identify another primary pathogen.

(4) **Leptospirosis**
(a) Clinical findings and diagnostic plan. Leptospires are slender spirochetes that require special laboratory techniques to stain and detect. Leptospires may be identified in body fluids (usually urine) by dark-field microscopy, immunofluorescence, or DNA hybridization. Single high (greater than or equal to 100:1 dilution) or a fourfold increase in paired samples on the microscopic agglutination tests are considered diagnostic.
(b) Etiology. Clinical disease is caused by serovars of Leptospira *interrogans.* Serovars hardjo and kennewicki (formerly *pomona*) are responsible for disease in ruminants.
(c) Pathogenesis. A maintenance host (cattle for variant hardjo; wild mammals for variant *kennewicki*) infects moist soil and pools of water. The organism may be ingested or penetrate intact skin. Acute disease coincides with the subsequent leptospiremia. Among other pathogenic mechanisms, cold-agglutinating IgM attaches to host erythrocytes, leading to intravascular hemolysis.
(d) Therapeutic plan. Intravenous fluid therapy should be initiated. Patients may require treatment for acute renal failure (see Chapter 15), disseminated intravascular coagulation [DIC; see II B 3 b (5)], or both. Antibiotic therapy includes penicillin initially, followed by dihydrostreptomycin or tetracycline therapy when renal function has returned to normal.
(5) Bacillary hemoglobinuria is very similar to Black's disease (see Chapter 5 III A 3).
(a) Clinical findings. Affected ruminants often are found dead due to peracute disease. Other affected animals are extremely depressed, walk with hunched backs, and are very sensitive to abdominal palpation. Normal bodily functions are reduced or absent. Tachycardia, tachypnea, and fwer are common. Animals that survive more than 1 day may have icterus and hemoglobinuria, and icteric tissues are commonly found on postmortem examination.
(b) Etiology and pathogenesis. Clostridium *hemolyticum* is a large, spore-forming, gram-positive anaerobic rod. Spores survive in the environment for a long time, are ingested or inhaled, and are transported to the liver of ruminants. With hepatic injury, commonly due to fluke migration, spores germinate. Mature bacteria produce exotoxins, which cause local necrosis and intravascular hemolysis.
(c) Diagnostic plan and laboratory tests. Postmortem examination, revealing severe hepatic necrosis with infarcts, hemorrhagic exudates, and subcutaneous edema, is strongly suggestive of this disease. The organism may be found by bacteriologic culture or impression smear of liver lesions. Hemoglobinuria should be present.
(d) Therapeutic plan. Treatment is rarely rewarding. If pursued, treatment should consist of large doses of penicillin and supportive care.
(e) Prevention. Vaccination with clostridial toxoids and fluke prevention are both efficacious in preventing this disease.
(6) Yellow lamb disease
(a) Patient profile. This hemolytic disease has only been identified in lambs.
(b) Clinical findings. Affected lambs are depressed, weak, and often in distress. Anemia, icterus, and hemoglobinuria are common.
(c) Etiology and pathogenesis
(i) Etiology. *Clostridium perfringens* type A, the causative agent, is a large, spore-forming, gram-positive anaerobic rod. Spores survive for long periods in the soil, and the organism may inhabit the gut of healthy animals.
(ii) Pathogenesis. The organism proliferates in the gut and releases exotoxins. One of these exotoxins, the a-toxin, causes vasculitis and intravascular hemolysis due to phospholipase activity.
(d) Therapeutic plan. Most affected lambs die within 12 hours of the onset of

clinical signs. Treatment with large doses of penicillin and supportive care can be attempted.
(e) Prevention. There is no toxoid useful in preventing this disease.
b. Immune-mediated causes of HA
(1) **NI**
(a) Patient profile. NI does not occur without human intervention in cattle, sheep, or goats. There is no breed or sex predisposition.
(b) Clinical findings. Clinical signs usually develop within 24–36 hours postpartum. Sudden loss of appetite and weakness are seen. Death usually occurs within 24 hours. The animal may show anemia, tachycardia, and rapid or shallow breathing, which progresses to labored breathing.
(c) Etiology. This immune-mediated RBC destruction in neonates is associated with the ingestion of colostrum containing antibodies to the neonates' erythrocytes.
(d) Pathogenesis. Blood transfusion or the administration of whole erythrocyte vaccines (such as those against anaplasmosis and babesiosis) to breeding females may sensitize the dam to certain blood groups, most commonly in the A and F systems. If the blood types of the sire and offspring contain these antigens and the dam has produced alloantibodies against them, an immune-mediated hemolytic crisis may appear in the calf associated with successful passive transfer.
(e) Diagnostic plan and laboratory tests
(i) Clinical pathology reveals a low PCV, hypoproteinemia, and high (conjugated) bilirubin. In sheep, NI may be more of an extravascular hemolysis.
(ii) A direct Coornbs' test should be performed.
(f) Therapeutic plan. Treatment consists of blood transfusions or intravenous fluids.
(2) Bovine colostrum fed to sheep
(a) Patient profile. Disease is usually seen in lambs between the ages of 7 and 21 days that are fed bovine colostrum. No sex or breed predisposition has been reported.
(b) Clinical findings. Clinical signs include a sudden loss of appetite and weakness, without evidence of icterus or hemoglobinuria. Death may occur in less than 24 hours.
(c) Etiology. Immune-mediated destruction of sheep RBCs may occur because of antibodies directed against sheep blood group antigens, which are present in bovine colostrum.
(d) Pathogenesis. The presence of antibodies to sheep blood group antigens in bovine colostrum is a common occurrence. These antibodies are called "heterophile antibodies" and result from the production of antibodies to common cross-reactive antigens that are present on the surfaces of bacteria and protozoa. When bovine colostrum is fed to lambs, these antibodies bind to sheep RBCs and lead to extravascular destruction.
(e) Diagnostic plan and laboratory tests
(i) A direct Coornbs' test with anti-sheep immunoglobulin and anti-bovine immunoglobulin may demonstrate immunoglobulin on the surface of RBCs.
(ii) **Direct immunofluorescence** may also demonstrate antibodies.
(iii) Clinical pathology reveals anemia, hypoproteinemia, icteric plasma, and hyperbilirubinemia (73% unconjugated). Hemoglobinemia or hemoglobinuria are usually not seen.
(f) Therapeutic plan. Whole blood transfusions or intravenous fluids may be necessary.
c. Toxic causes of HA
(1) *Brassica* species plants (e.g., kale, canola)
(a) Patient profile. Cattle appear to be more sensiiive to *Brassica* plants than horses or small ruminants.
(b) Clinical findings. The severity of clinical signs relates to the duration and

dose of feeding the toxin. Because oxidant damage to erythrocytes usually results in extravascular hemolysis, only cows with a concomitant disease, which increases erythrocyte fragility (postparturient hemoglobinuria), should have intravascular hemolysis and hemoglobinuria.

(i) Most affected animals exhibit pallor, weakness, decreased milk production, dark urine, and mild to moderate **icterus.**

(ii) Neurologic signs and pulmonary emphysema are seen occasionally in cows fed Brassica plants, but the mechanism is unknown.

(c) Etiology and pathogenesis

(i) The toxin content of Brassica plants increases as these plants mature but is destroyed by heating or ensilage. Feeding these plants worsens the hemolytic crisis seen with postparturient hemoglobinuria [see I D 2 d (2)].

(ii) Brassica plants contain S-methyl cysteine sulfoxide, which is metabolized by rumen bacteria to dimethyl disulfide. This toxin decreases the activity of glutathione within erythrocytes, allowing disulfide bonds to form between hemoglobin chains, resulting in Heinz body formation. As erythrocytes containing Heinz bodies are removed by the reticuloendothelial system, anemia develops.

(d) Diagnostic plan and laboratory tests. Feeding history, clinical signs, and the identification of Heinz-body anemia are critical to making a diagnosis. Dimethyl disulfide concentration in blood or rumen fluid can be measured using gas chromatography.

(e) Therapeutic plan. The removal of animals from the feed and blood transfusions for severely affected animals are the only treatments.

(2) Onion

(a) Patient profile **and history.** Cattle appear to be more sensitive to onions than other farm animals. History of exposure to onions is important in establishing a diagnosis.

(b) Clinical **findings.** Affected animals can develop clinical signs within 1 week of being fed an all-onion diet.

(c) Pathogenesis. The toxic principle of onions is n-propyl disulfide, which causes Heinz-body anemia by the same mechanism as Brassica plants [see I D 2 c (1)]. S-methyl cysteine sulfoxide has also been reported to be found in onions.

(d) Therapeutic plan. Treatment is the same as that for ***Brassica*** toxicosis [see I D 2 c (1) (e)].

(e) Prevention. Clinical disease can be prevented by mixing onions with other feedstuffs so that onions compose less than 25% of the dry matter of the ration. However, cattle fed as little as 5% onions have laboratory evidence of HA.

(3) Copper

(a) Clinical findings. Severely affected animals have **icterus,** hemoglobinuria, weakness, and thin, watery blood. Vomiting and sudden death may also be observed. If mucous membranes are not severely jaundiced, pallor may be seen.

(b) Etiology and pathogenesis. Ingestion or injection of a toxic dose of copper can precipitate an acute episode of intravascular hemolysis. A similar syndrome is seen in animals that are chronically overfed copper. It is thought in this latter circumstance that hepatic saturation or another stress leads to the massive release of liver copper stores into the **blood.**

(c) Diagnostic plan and laboratory tests. Feeding or treatment history and clinical signs are strongly suggestive of this disease. For confirmation, copper concentrations in blood, liver, and feed can be determined.

(d) Therapeutic plan. Except for supportive care, most treatments for copper toxicosis are experimental.

(4) Nitrate and **nitrite** toxicosis

(a) Clinical findings

(i) Acute toxicosis. Clinical signs of acute nitrite toxicosis begin within

6 hours of ingestion of toxic feedstuffs. Animals display signs compatible with severe anoxia, including weakness, depression, cyanosis, and tachycardia. Animals die if 60%–75% of hemoglobin is oxidized to methemoglobin (this usually occurs within 24 hours of ingestion). Gastrointestinal signs include salivation, diarrhea, and vomiting.

(ii) Chronic toxicosis has been blamed for abortion and an increased vitamin A requirement.

(b) Etiology. Cereal crops, ***Astragalus*** plants, other plants, and deep water wells may accumulate nitrate, particularly in areas where nitrogenous fertilizers are used heavily.

(c) Pathogenesis. Nitrate is reduced to nitrite in the rumen. Heat may also reduce nitrate, so that hay stacked in strong sunlight or heat-prepared feedstuffs may contain nitrites and cause toxicosis in nonruminants. Absorbed nitrite oxidizes hemoglobin to methemoglobin and causes mild vasodilation. These effects result in tissue anoxia and hemolysis. Nitrates also cause gastroenteritis.

(d) Diagnostic plan and laboratory tests

(i) Clinical findings, history of exposure to nitrate-accumulating plants, and inspection of blood for methemoglobinemia are strongly suggestive of the disease.

(ii) A diphenylamine test can be performed on blood, urine, or feed (the inside of the plant stalk or rodt is best) to detect toxic nitrate levels. Tests on animal tissue must be performed quickly because nitrite is converted to other compounds.

(e) Therapeutic plan. Methylene blue (1% solution) can be given to reduce methemoglobin to hemoglobin. A single treatment (1–2 mg/kg of body weight given intravenously) is usually sufficient in nonruminants, whereas higher doses (up to 20 mg/kg) and repeated dosing (every 8 hours) may be necessary in ruminants that have ingested large quantities of nitrates.

d. Other causes of HA

(1) Water intoxication

(a) Clinical **findings.** This is primarily a neurologic disease. Affected animals show apparent–blindness; a staggering gait, dullness, and head pressing. Severely affected animals often have seizures and become comatose. Hemoglobinuria is seen in some cases.

(b) Etiology. Water intoxication occurs when free access to water is allowed after a period of deprivation. The condition is more severe if the animal has become dehydrated or is fed a high-sodium diet.

(c) Pathogenesis. With water deprivation, there is a gradual increase in the plasma sodium concentration due to insensitive water loss and an inability to excrete excess ingested salt. There is also a gradual increase in the sodium concentration in the brain and cerebrospinal fluid (CSF), although this occurs slowly because of the relative impermeability of the blood–brain barrier to sodium. When the animal is re-exposed to water, a rapid drop in plasma osmolality can cause osmotic lysis of RBCs and rapid transfer of free water into the brain. These result in intravascular hemolysis and cerebral edema, which lead to hemoglobinuria and neurologic signs, respectively.

(d) Diagnostic plan and laboratory tests. Information concerning diet and access to water helps confirm a diagnosis of water intoxication. Hemoglobinuria and the detection of a substantially higher CSF sodium concentration are also of diagnostic value. (There is usually a 10 mEq/L difference between the CSF sodium concentration and the plasma sodium concentration.)

(e) Therapeutic plan

(i) Treatment of comatose and seizing animals is rarely successful.

(ii) In less severely affected animals, the goal is to normalize the plasma and CSF sodium concentrations without causing rapid shifts in

water. This can be accomplished through limited access to free water and slow administration of intravenous fluids. Fluids containing sodium concentrations close to that in normal plasma are preferable to 0.45% sodium chloride solutions. Administration of full-strength solutions are less likely to cause pathologic rapid decreases in plasma osmolality.

(2) Postparturient hemoglobinuria

(a) Patient profile. Cattle in the first 6 weeks of lactation are most susceptible. Herd outbreaks can occur, although the disease usually affects single cows.

(b) Clinical findings. Affected cattle have red urine, pale mucous membranes, absent scleral vessels, tachycardia, tachypnea, weakness, and decreased milk production. Clinical signs last several days, and icterus may be seen toward the end of the disease course. Tissue anoxia or renal damage can cause death.

(c) Etiology and pathogenesis

(i) Etiology. The cause of this disorder is unknown and may differ in different parts of the world.

(ii) Pathogenesis. Increased erythrocyte fragility in postpartum dairy cows leads to intravascular hemolysis, anemia, and hemoglobinuria. In North America, hypophosphatemia is thought to impair function of the Na^+/K^+ pump, causing erythrocyte lysis. In New Zealand, hypocupremia is thought to make erythrocytes more sensitive to the hemolyzing activity of oxidant-containing plants.

(d) Diagnostic plan and laboratory tests. Clinical findings aid in the diagnosis. Laboratory tests can be used to confirm hemoglobinuria and to investigate underlying mineral deficiencies.

(e) Therapeutic plan

(i) Blood transfusion. Severely affected animals should be transfused with fresh whole blood.

(ii) Fluids. If blood is unavailable, crystalloid fluids can be used to increase cardiac output and protect the kidneys against the toxic effects of hemoglobin.

(iii) Phosphorus or copper supplements can be administered, if indicated, and efforts should be made to avoid feeding oxidant-containing plants.

(3) Inherited congenital porphyria

(a) Clinical findings. Plasma and urine from affected animals are red or reddish brown. Photosensitization of unpigmented skin occurs in cattle exposed to direct sunlight Teeth and bones may have a pink or brown discoloration and fluoresce red on exposure to ultraviolet (UV) light.

(b) Etiology and pathogenesis. Congenital porphyria appears to be an autosomal recessive defect of cattle. Similar diseases in people are caused by the insufficiency of an enzyme in the pathway of heme synthesis. As a result, hemoglobin synthesis and RBC maturation are impaired, and porphyrins accumulate in body fluids and tissues. Anemia results both from impaired erythrocyte production and hemolysis. Porphyrin pigments are red or brown and act as photosensitizing agents.

(c) Diagnostic plan and laboratory tests. Clinical features are strongly suggestive of this disease.

(i) Histopathologic examination of bones and teeth reveals large amounts of porphyrin pigments. Porphyrin pigments may be identified in urine by spectroscopic examination.

(ii) Anemia is usually characterized by macrocytosis and normochromasia due to impaired erythrocyte production.

(d) Therapeutic plan. Affected cattle should be shielded from direct sunlight. There is no other specific treatment.

3. **Eperythrozoonosis** of swine

a. Clinical findings. During the acute reaction, affected pigs are febrile and have a rapidly decreasing PCV.

(1) Adult pigs are depressed and inappetent.

(2) Lactating sows may have reduced milk production.

(3) Piglets less than 2 weeks old and feeder pigs may have weakness, detectable pallor and icterus, and poor growth.

b. Etiology and pathogenesis

(1) Etiology. Disease is caused by the rickettsial organism *Eperythrozoon suis,* which is an obligate parasite of RBCs and is thought to be spread by arthropods.

(2) Pathogenesis. Organisms initially multiply rapidly within erythrocytes. The body's immune response leads to the coating of infected RBCs with cold-agglutinating IgM. These cells are removed in reticuloendothelial organs, causing extravascular hemolysis and anemia.

c. Diagnostic plan and laboratory tests. Identification of round, dark-staining organisms within RBCs on **Giemsa-stained** blood **smears** is the most common form of diagnosis. There are also serologic tests for eperythrozoonosis.

d. Therapeutic plan. Spontaneous recovery is common, but infected pigs rarely reach full growth potential, and some may be chronic carriers of the organism.

(1) Injections. Clinical signs usually resolve after a single shot of a long-acting tetracycline. A second injection may be necessary in some cases.

(2) Tetracycline feed additives usually are ineffective because of decreased intake, but water supplements have proved beneficial. These same protocols may improve performance of chronically infected animals.

e. Prevention. Arthropod control (i.e., ivermectin for mites) should be improved in piggeries with endemic eperythrozoonosis.

E. Depression anemia. Reduced bone marrow production is a common cause of mild nonregenerative anemia in large animals. There are several possible causes of reduced production.

1. Nutritional deficiency anemia

a. Iron deficiency

(1) History. Iron deficiency is most commonly seen with chronic blood loss due to parasitism but is also a common finding in calves on an all-milk diet or neonates (particularly piglets) housed without access to dirt.

(2) Pathogenesis. Iron is necessary for hemoglobin synthesis, and iron deficiency leads to a decrease in hemoglobin production.

(3) Diagnostic plan and laboratory tests. Iron-deficient animals typically exhibit:

(a) Low iron stores visible in marrow stained with Prussian blue stain

(b) High serum iron-binding capacity with low serum iron concentrations

(c) Microcytic hypochromic anemia

(4) Therapeutic plan. Supplemental iron may be given orally (ferrous sulfate) or parenterally (iron dextran or cacodylate), but these treatments have been associated with fatal reactions.

b. Copper deficiency. Copper is vital for iron transport; thus, copper deficiency anemia resembles iron deficiency anemia. Copper deficiency also may be a factor in some cases of postparturient hemoglobinuria.

(1) Etiology. This deficiency may be primary or secondary to dietary excesses in molybdenum, sulfates, or zinc.

(2) Clinical findings. Copper deficiency causes anemia, ill thrift, dilute hair color, chronic diarrhea, and neurologic disease.

(3) Diagnostic plan and laboratory tests. Copper levels can be measured in serum, liver tissue, or hair.

(4) Therapeutic plan. Supplemental copper may be given orally or parenterally.

c. Cobalt, folate, and vitamin B_{12} deficiency

(1) Clinical findings. Cobalt or vitamin B_{12} deficiency is associated with ill thrift, weight loss, poor growth, and anemia. Anemia is usually normocytic, normochromic, and probably associated with impaired protein and energy metabolism. Macrocytosis may also be seen.

(2) Etiology and pathogenesis

(a) Etiology. Inadequate dietary cobalt results in inadequate ruminal vitamin B_{12} production in ruminants. Horses require preformed vitamin B_{12} in their diets.

(b) Pathogenesis. Vitamin B_{12} is necessary in all large animal species for folate metabolism and is necessary in ruminants for gluconeogenesis from propionate. Deficient folate metabolism leads to impaired erythrocyte maturation.

(3) Diagnostic plan and laboratory tests. Diagnosis of cobalt deficiency can be established bv the measurement of vitamin B_{12} concentrations in serum or liver tissue.

(4) Therapeutic plan. Supplemental vitamin B_{12} can be given parenterally, or cobalt can be added to the diet.

2. Anemia of chronic disease

a. Clinical findings. Affected animals have mild **normocytic** normochromic anemia and low serum iron concentration and binding capacity.

b. Etiology and pathogenesis. Chronic inflammatory reactions appear to cause mild anemia by altering iron metabolism. **Iron** is stored in a nonuseful form. Shortened erythrocyte **lifespan** may also contribute to the anemia.

c. Diagnostic plan and laboratory tests. Prussian blue staining of marrow reveals adequate iron stores, but much of the iron appears to be unavailable for heme **synthesis**.

d. Therapeutic plan. Treatment efforts should be directed toward the primary disease.

3. Anemia secondary to organ dysfunction

a. Overview. In addition to the effects of chronic disease, dysfunction of specific organs can lead to nonregenerative anemia.

(1) Cut function is necessary for the absorption of essential nutrients.

(2) Liver function is necessary for the proper distribution of nutrients.

(3) Liver and kidney function together are necessary for the adequate production of erythropoietin, the major stimulus for **erythropoiesis.**

b. Therapeutic plan

(1) Treatment efforts are usually directed toward the primary **disease.**

(2) Recombinant **erythropoietin** therapy may prove to be of some value in **treating** depression anemia in large animals.

4. Anemia secondary to bone marrow dysfunction or **dysplasia**

a. **Clinical findings.** Because erythrocytes are among the longest-lived blood cells (more than 140 days in most large animals), neutropenia, **thrombocytopenia,** and their clinical **effects (e.g.,** infection, hemorrhage) may be seen before anemia **develops.**

b. Etiology. All normal blood cells are generated through the hyperplastic activity of stem cells in the marrow. Replacement of lost cells may be insufficient if there are too few stem cells, or if the activity of those cells is **suppressed.**

(1) The most common cause of loss of stem cell populations is crowding **out** through the proliferation of a neoplastic cell line. In all large animals, the most common neoplasm associated with marrow destruction is **lymphoma.**

(2) Suppression of stem cell hyperplasia, aplastic anemia, is most commonly an idiosyncratic reaction to a drug or toxin. Nonsteroidal anti-inflammatory drugs **(NSAIDs; e.g., phenylbutazone),** synthetic estrogens, and bracken **fern** toxicosis (in cattle) have been associated with aplastic anemia.

c. Diagnostic plan and laboratory tests

(1) Blood work. Anemias caused by suppression or replacement of bone marrow are usually normocytic and normochromic, with minimal evidence of a regenerative response.

(2) Cytologic examination of bone marrow. Because animals affected by these processes frequently have a chronic disease, differentiation between anemia secondary to bone marrow dysfunction or dysplasia and anemia of chronic disease is difficult and **best** achieved by cytologic evaluation of bone marrow.

(a) With anemia of chronic disease, the bone marrow contains numerous stem cells and frequently contains large iron stores, although evidence of active hyperplasia and maturation is less than expected.

(b) With anemia caused by crowding out of the marrow, stem cell lines are present in small numbers and another neoplastic cell line is also present.

(c) With suppression of bone marrow, stem cells are present, but evidence of hyperplasia and maturation is minimal.

d. **Therapeutic** plan

(1) When marrow suppression is suspected to be caused by a drug or toxin, the animal should be removed from the source of that drug or toxin.

(2) If marrow cells have been crowded out by neoplastic cells, chemotherapeutic agents may be administered to treat the neoplastic process.

(3) There are currently no specific therapeutic agents licensed for use **in stimulating** marrow hyperplasia in large animals. **If** nonerythroid cell lines [white blood cells **(WBCs),** platelets] are affected, fresh plasma or whole blood administration and prophylactic antibiotic administration may be beneficial. Treatments used in humans and small animals, including marrow transplants and administration of synthetic hormonal stimuli for marrow activity (colony stimulating factors) are currently impractical for use in large animals, but may be available in the future.

III. **HEMOSTATIC** DYSFUNCTION

A. **Petechial** hemorrhages

1. **Vasculitis**

a. Equine purpura hemorrhagica (EPH)

(1) History. Typically horses with EPH have a history of respiratory infection 2–4 weeks before the onset of clinical signs. Respiratory infections may be caused by Streptococcus ***equi,*** Streptococcus ***zooepidemicus,*** or equine influenza virus.

(2) Clinical finding. This condition is characterized by fever and edema, **primarily** of the limbs and sometimes the head, ventral abdomen, thorax, and **prepuce**. Occasionally, horses are depressed. Lymphadenopathy may be found. Sometimes, petechial hemorrhages are seen on **mucosae.** Wheals may occur and **glomerulonephritis** has occasionally been reported. Colic associated with hemorrhage, edema, and necrosis of the intestinal wall has been reported. Affected horses may be reluctant to move.

(3) Etiology. The cause is unknown, but the disorder may be **associated** with an allergic reaction to streptococcal or viral antigens.

(4) Pathogenesis. EPH is an immune complex-mediated disease. ***S. equi*** **or** other antigens bind to specific antibodies, particularly **IgA,** leading to immune complex formation. These complexes are deposited in vessel walls, with **subsequent** complement activation and chemoattractant production. Infiltrating in**flammatory cells** release proteolytic enzymes that cause vessel-wall necrosis, with subsequent edema, hemorrhage, and infarction of supplied tissues. Death may occur.

(5) Diagnostic plan and laboratory tests

(a) A history of recent respiratory tract infection and clinical signs lead to a diagnosis. Isolation of a respiratory pathogen from the upper respiratory tract or pharyngeal lymph node is supportive of a diagnosis.

(b) A skin biopsy may reveal **leukocytoclastic** venulitis.

(c) Serum levels. Horses have elevated levels of serum **IgA** with normal **IgG** and **IgM** levels.

(6) Therapeutic plan. Treatment is directed at removing the antigenic stimulus, re**ducing** the immune response, reducing vessel wall inflammation, and **providing** supportive care.

(a) Edema can be minimized by hydrotherapy, the application of pressure wraps, and the administration of diuretics.
(i) NSAIDs may reduce inflammation and provide analgesia.
(ii) High doses of dexamethasone may be required initially.
(iii) Antimicrobial therapy may reduce the incidence or severity of cellulitis and other septic sequelae.
(iv) Intravenous fluids may be required to prevent dehydration.
(b) Isolation. Affected horses should be isolated for 4–5 weeks or until there are three negative nasal swab cultures.
(7) Prognosis. The prognosis for EPH is fair with early, aggressive therapy and supportive care. Possible complications include skin sloughing, laminitis, cellulitis, pneumonia, and diarrhea.
(8) Prwention. There is no means of prevention other than avoiding exposure of previously sensitized horses to antigens such as *S. equi*.

b. Equine viral **arteritis** (EVA)
(1) Patient profile. The host range of EVA is restricted to equids. The disease is widely distributed in horse populations throughout the world. EVA infection is endemic in Standardbreds, although there does not appear to be any difference in susceptibility to infection between the Standardbred horses and other breeds.
(2) Clinical findings
(a) Subclinical infections with EVA are very common, particularly in mares that are bred to carrier stallions. No carrier state has been demonstrated in the mare. Abortion with no other clinical signs can occur between 3 and 10 months' gestation.
(b) Clinical **signs** may include pyrexia (up to 41°C) that can last 2–9 days, depression, anorexia, leukopenia, limb edema (particularly of the hind limbs), stiffness of gait, nasal and lacrimal discharges, conjunctivitis, periorbital edema, and ventral edema involving the scrotum, prepuce, or mammary gland.
(3) Etiology. The causative agent is a non–arthropod-borne group of togaviruses in the genus *Arterivirus.* Only one major serotype of the virus has been recognized.
(4) Pathogenesis. Exposure to EVA may result in the development of clinical or inapparent infection, depending on the strain of virus involved, size of the virus challenge, the age and physical condition of affected animals, and environmental contamination. Except for the potential of abortion, mortality does not occur following infection with naturally occurring strains of EVA.
(a) Transmission
(i) Inhalation of infectious aerosolized particles is the primary means of transmission during outbreaks.
(ii) Venereal infection of a long-term carrier stallion represents the primary means whereby EVA is maintained in horse populations. Venereal transmission to a susceptible mare can trigger an outbreak of the disease.
(iii) Rarely, **transplacental** transmissions of EVA can occur when a pregnant mare is exposed to the virus during gestation. If infection occurs during late gestation, the fetus can acquire the. infection. Infected foals are aborted after developing rapidly progressive fulminating interstitial pneumonia and a fibrinonecrotic enteritis.
(b) Viral growth. Initial multiplication of the virus occurs in bronchial macrophages in the lung. Within 48 hours of infection, EVA disseminates to regional lymph nodes, and by the third day, viremia develops.
(c) Disease progression. Characteristic vascular lesions first appear in the pulmonary blood vessels and later in the small arteries and veins throughout the body. The virus localizes in some epithelial sites, particularly the adrenal gland, seminiferous tubules, thyroid gland, and liver. The virus can persist in the reproductive tract long after it is no longer detectable in most body fluids.

(5) Diagnostic plan and laboratory tests. Both clinical and inapparent EVA infections often go undiagnosed due to limitations in available diagnostic capability and because the disease can be readily confused with other clinically similar respiratory diseases of horses.
(a) Acute EVA. Confirmation of a diagnosis of acute EVA is based on viral isolation, corroborative serologic data, or both.
(i) Serologic tests. Acute and convalescent sera samples should be taken 21–28 days apart. A fourfold rise in antibody titers is suggestive of an acute infection.
(ii) Viral isolation can be done on nasopharyngeal swabs or washings, conjunctival swabs, and citrated, ethylenediamine tetraacetic acid (EDTA), or heparinized blood samples. Virus isolation can be attempted from placental and fetal fluids, placenta, lymphoreticular organs, lung, and other tissues.
(b) Identifying carrier stallions can be done by serologic testing. Horses testing positive at a serum dilution of 1:4 or greater should be considered potential carriers of the virus. Isolation of the virus can be attempted from a semen sample. The virus is usually found in the sperm-rich fraction of the ejaculate.
(6) **Therapeutic** plan
(a) There is no **specific** treatment for hones infected with EVA. Spontaneous recovery usually occurs within 4 weeks.
(b) Symptomatic therapy, including rest, diuretics, and NSAIDs, may be helpful to counteract edema and pyrexia.
(7) Prwention
(a) Vaccination. A modified-live vaccine appears to be safe and effective for stallions and nonpregnant mares. This vaccine is not recommended for pregnant mares or foals younger than 6 weeks of age.
(i) Protection after vaccination lasts for at least 1–3 years. However, it does not prevent reinfection and limited replication of the challenge virus.
(ii) Vaccinated horses cannot be distinguished from infected horses by serologic tests and, therefore, cannot be transported when a negative titer is required.
(b) Isolation. In order to reduce the chances of introducing EVA into a group of susceptible horses, all horses returning from other farms, sales, or racetracks should be isolated for 3–4 weeks. In the event of an outbreak of EVA, the movement of breeding stock should be restricted. Selective vaccination may help curtail the spread of disease.
(c) Control programs. Kentucky and New York are the only states that have formulated preventative and control programs for their respective Thoroughbred breeding industries.

c. Equine ehrlichiosis
(1) Patient profile. There **appears** to be a seasonal incidence of infection, with most cases occurring during the fall, winter, and early spring.
(2) Clinical findings. Clinical signs vary according to the age of the affected horses.
(a) In horses younger than 1 year old, fever may be the only sign.
(b) Horses ages 1–3 years may develop fever, depression, limb edema, and ataxia.
(c) Horses older than 3 years often are most severely affected. Clinical signs include anorexia, depression, severe limb edema, fever, **mucosal petechiation**, and restricted movement
(3) Etiology and pathogenesis
(a) Etiology. The causative agent is ***Ehrlichia equi*****,** a **rickettsial** organism.
(b) Pathogenesis
(i) The mode of transmission is unknown, but, in most cases, affected horses have been exposed to or infested with ticks.

(ii) After natural infection, the incubation period is unknown. Experimentally infected horses develop clinical signs in 1–9 days.
(iii) *E. equi*-organisms live in the cytoplasm of neutrophils and eosinophils and cause a necrotizing vasculitis in many parts of the body.

(4) Diagnostic plan and laboratory tests
(a) **Giemsa-** or Wright-stained blood smears demonstrate the characteristic cytoplasmic inclusion bodies in neutrophils or eosinophils.
(b) **Indirect** fluorescent antibody testing, using paired serologic samples, can also be used.

(5) Therapeutic plan. Intravenous administration of **oxytetracycline** can be used. Recovery usually occurs within 10 days with supportive care, including NSAIDs.

(6) Prognosis is excellent in uncomplicated cases.

2. **Thrombocytopenia**

a. Clinical findings. Thrombocytopenia often results in petechial hemorrhages in the mucous membranes. Hematuria, epistaxis, and melena may be seen.

b. Etiology and pathogenesis. Thrombocytopenia may be the result of platelet consumption, decreased platelet production, or platelet destruction.
(1) Platelet consumption is most common with septic conditions or DIC.
(2) Decreased platelet production is most common with aplastic anemia or infiltration of the marrow with neoplastic cells.
(3) Platelet destruction (in addition to that caused by consumption) usually occurs through an immune-mediated process. Drug treatments (particularly penicillin), lymphosarcoma, and systemic bacterial infections are the most commonly described triggers for immune-mediated thrombocytopenia. In many animals, a source cannot be identified.

c. Diagnostic plan and laboratory tests
(1) Platelet counts are usually very low (less than 40,000/μL). Overt hemorrhage may be seen if platelet counts drop below 10,000/μL.
(2) Total clotting time is prolonged, but activated partial thromboplastin time and prothrombin time should be normal.
(3) Measurement of **antiplatelet** antibodies is not currently practical for large animals, so the diagnosis often is based on the response to treatment. Efforts should be made to find an underlying disorder.

d. Therapeutic plan. All medications should be discontinued. If the action of a particular drug is essential, a different class of drug (anti-inflammatory or antibiotic) should be used, if possible.
(1) **Immunosuppressive** drug treatment. When immune-mediated thrombocytopenia has been diagnosed and all identified underlying factors have been removed or treated, a course of an immunosuppressive drug (usually dexamethasone) can be given. A 2- or 3-week course with decreasing dosages is usually sufficient, but platelet counts should be monitored to determine that the disease is in remission before immunosuppressive treatments are discontinued.
(2) Fresh whole blood or platelet-rich plasma can be used to immediately increase platelet counts in animals with severe thrombocytopenia.

B. Abnormal hemorrhage from large vessels

1. Overview. This disorder almost always reflects a defect in the coagulation cascade and is, therefore, independent of platelet function. However, platelet dysfunction can be present and may contribute to bleeding tendencies.

a. Clinical findings. Clotting deficiencies can result in excessive bleeding after trauma or surgery, bleeding into body cavities (e.g., hematoma, hemoperitoneum, hemothorax, hemopericardium, hemarthrosis), or bleeding from epithelial surfaces (e.g., epistaxis, hematuria, melena, hematochezia).

b. Etiology. Coagulopathies can be inherited or acquired. Acquired coagulopathies can result from toxins, infections, trauma, or neoplasms.

2. Inherited coagulative disorders

a. Pathogenesis. All inherited clotting factor deficiencies affect the intrinsic pathway and, therefore, prolong the activated partial thromboplastin time (APTT) but not the prothrombin time (PT).

b. Therapeutic plan. Except for periodic transfusion with fresh plasma, specific treatments are not available.

c. Specific conditions
(1) Deficiencies in factors VIII, IX, XI, and prekallikrein have been described in horses.
(a) Factor VIII deficiency (hemophilia A) is sex-linked and recessive.
(b) Inheritance patterns for the other deficiencies are not known.
(2) Factor XI deficiency has been described in Holstein cows and is thought to have an autosomal recessive pattern of inheritance.
(3) Factor XI deficiency causes only slight bleeding tendencies.

3. Acquired coagulative **disorders** are usually related to a lack of production, consumption, or inhibition of clotting factors. Because multiple factors are affected, both the intrinsic and extrinsic pathways are impaired.

a. **Inhibition** of vitamin K-dependent factors
(1) Sweet clover
(a) Pafient profile. Cattle appear to be more sensitive than sheep or horses.
(b) Clinical finding. Clinical signs are caused by internal or external hemorrhage. External hemorrhage can lead to anemia, weakness, and hypovolemic shock, whereas internal hemorrhage additionally leads to subcutaneous swelling and pain. Spontaneous hemorrhage is rare and usually results from a traumatic insult, such as calving or dehorning.
(c) Pathogenesis. Coumarol, which is normally found in sweet clover, can be converted to dicoumarol by molds during spoilage. Dicoumarol inhibits the synthesis of the vitamin K-dependent coagulation factors (factors VII, IX, X, and prothrombin), leading to bleeding tendencies. Chronic feeding either of spoiled hay or silage is usually necessary to cause clinical signs, with hay more likely to contain toxic concentrations of dicoumarol than silage.
(d) Diagnostic plan and laboratory tests
(i) Evidence of internal or external hemorrhage with history of exposure to moldy sweet clover feeds is indicative of dicoumarol toxicosis.
(ii) Abnormal tests of clotting function in animals exposed to the feeds is also supportive. Determination of prothrombin time is the most accurate of these clotting function tests.
(iii) **Feed** samples should be submitted for analysis to determine dicoumarol content. Multiple samples should be analyzed because dicoumarol production may be localized.
(e) Therapeutic plan
(i) Transfusion. Animals with severe anemia or hypovolemic shock should be treated with whole blood, if possible.
(ii) Crystalloid fluids should be administered to animals in shock if blood is not available. Feeding of the affected feedstuffs should be discontinued immediately.
(iii) Vitamin K_1 and K_3 have both been shown to reduce prothrornbin times in cattle with dicoumarol toxicosis; Vitamin K_1 appears to be more effective.
(f) Prevention. Efforts should be made to reduce moist aerobic conditions in sweet clover products. Moldy hay and silage should not be fed. If all suspected feed cannot be discarded, it should be fed in combination with other feeds and fed intermittently. Cattle appear to be able to maintain normal coagulation function if they are completely removed from affected feed every second or third week.

(2) Warfarin toxicosis
(a) Patient profile. Pigs appear to be the most susceptible farm animal species because of their small size and eating behavior.
(b) Clinical findings. Overt hemorrhage and rapid death may occur with massive dosages. Chronic exposure to smaller dosages causes a similar syndrome to moldy sweet clover.
(c) Pathogenesis. Warfarin is related to dicoumarol and also induces hypocoagulability by preventing the synthesis of the vitamin K-dependent clotting factors. Warfarin and related compounds are used as rodenticides. Large animal exposure can occur due to accidental ingestion of rodent bait or contaminated feed.
(d) Prevention. The source of the toxin should be determined to prevent subsequent exposure.

b. **DIC** is a disorder that may be characterized by widespread thrombosis, bleeding tendencies, or both.
(1) Clinical findings. The most notable signs usually are referable to the primary disease that triggers DIC.
(a) Organ thrombosis may contribute to morbidity and mortality. Clinical signs of thrombosis include weakness, colic, oliguria, and neurologic deficits.
(b) Bleeding tendencies (coagulopathy) rarely result in overt hemorrhage but may result in mucosal petechiation, melena, retinal hemorrhage, and prolonged bleeding from venipuncture sites.
(2) Etiology. The exact mechanism of DIC has not been described and may vary from case to case. It is generally accepted that a triggering insult leads to diffuse activation of the coagulation cascade. Triggering insults include:
(a) Sepsis
(b) Neoplasia
(c) Vasculitis
(d) Ischemia
(3) Pathogenesis. Diffuse coagulation can lead to thrombosis and ischemic damage to organs. Clotting factors and platelets are consumed in the process, leading to subsequent clotting deficits. With ensuing fibrinolysis, hemorrhage may occur.
(4) Diagnostic plan and laboratory tests. Because DIC can be characterized by either hypercoagulation or hypocoagulation, tests of cloning function may be normal or abnormal. However, the finding of thrombocytopenia and prolonged clotting times is suggestive of DIC, as are findings of low plasma antithrombin III concentrations with concurrent high fibrin degradation product concentrations.
(5) Therapeutic plan. Many treatments have been proposed for DIC, but most have not been evaluated critically. Treatment of the primary disorder is essential.
(a) Intravenous fluids help maintain organ perfusion and may decrease susceptibility to thrombosis.
(b) **Corticosteroids** and heparin may be contraindicated because of their unpredictable effects on coagulation. Low doses of **NSAIDs** may be helpful in some cases when endotoxin is thought to be an inciting factor for DIC.
(c) Treatment is generally unsuccessful if there is evidence of a hypocoagulable state.

c. **Suppression.** A lack of production of clotting factors is most common with severe chronic hepatic disease. Because factor VII has the shortest half-life, deficits in the extrinsic pathway are seen before there is overt hemorrhage. Animals with severe hepatic disease will have reduced blood coagulability, as measured by clotting assays and reduced plasma concentrations of most clotting factors, including fibrinogen. Coagulopathy is only one of many clinical signs seen in animals with severe chronic liver disease (see Chapter 5).

III. LYMPHATIC DISEASES

A. Lymphoproliferative and myeloproliferative disorders

1. Bovine **leukosis.** Lymphomas in cattle are characterized by the presence of soft tissue masses consisting of immature lymphocytes within a fibrous stroma. Bovine lymphomas can be subdivided into sporadic or enzootic, based on the etiology.
a. Sporadic lymphoma
(1) Overview
(a) Patient profile. Although small "outbreaks" have been reported, usually only single animals are affected.
(b) Clinical findings and diagnostic plan. Affected cattle may have serum titers against the bovine leukemia virus **(BLV)** due to transfer of maternal antibody or concurrent infection with the virus, but BLV is not thought to contribute to these diseases.
(c) Etiology and pathogenesis. No cell type, etiologic agents, or risk factors have been identified.
(d) Diagnostic plan and laboratory tests. Diagnosis is by histopathologic examination of tissue biopsies.
(e) Therapeutic plan. Treatment is rarely attempted.
(2) Specific conditions. There are three forms of sporadic lymphoma.
(a) juvenile **multicentric** lymphoma
(i) Patient profile. This sporadic lymphoma is seen in cattle younger than 2 years old (most commonly between ages 4 and 8 months).
(ii) Clinical findings. Affected calves develop fatal progressive weight loss, lymphadenopathy, and depression. Many different internal organs can be infiltrated. Half of affected calves develop lymphoid leukemia.
(b) Thymic lymphoma
(i) Patient profile. This disease is seen in cattle between ages 6 and 24 months.
(ii) Clinical findings. Affected calves die after developing presternal swelling, jugular distention, and local edema. Muffling of heart sounds and respiratory distress can be present with intrathoracic tumor growth. Leukemia is present in one-third of affected calves.
(c) Cutaneous lymphoma
(i) Patient profile. This lymphoma occurs in cattle between ages 1 and 4 years.
(ii) Clinical findings. Affected cattle develop multiple dermal or epidermal nodules, which can be covered by normal or hyperkeratotic skin. Cutaneous lesions may regress spontaneously, but most animals die of internal metastatic tumors.
b. **Enzootic** lymphoma
(1) Patient profile
(a) Prevalence of infected cattle in individual herds varies, but in general, dairy cattle are more likely to be infected than beef cattle. A variety of domestic and nondomestic ruminants are also reported to be susceptible.
(b) Approximately 30% of infected cattle develop persistent **lymphocytosis** (i.e., high peripheral blood counts of normal lymphocytes). Less than 10% of cattle infected with BLV develop lymphoma, and most of these are between ages 4 and 8 years.
(2) Clinical findings. Persistent lymphocytosis does not appear to predispose those cattle to subsequent tumor development.
(a) Tissue masses. The most common sites for tissue masses are the lymph nodes, abomasum, heart, uterus, kidney, lumbar spinal cord, and in the retrobulbar space. Multiple sites are usually affected.
(b) Nonspecific clinical signs include weight loss, decreased milk production, anorexia, and occasionally fever.
(c) Specific signs relate to the organs affected and can include

lymphadenopathy, signs of heart failure, exophthalmos, reproductive failure, melena, and posterior paresis.
(d) Death usually occurs within 30 days of the onset of clinical signs.
(3) Etiology and **pathogenesis**
(a) **Etiology.** Bovine enzootic or adult lymphoma is caused by BLV, an oncogenic retrovirus.
(b) **Pathogenesis.** The virus infects and replicates in B cells and appears to be spread by the introduction of infected lymphocytes into a susceptible host. Repeated use of blood-contaminated equipment, including dehorning tools, hypodermic needles, and rectal sleeves, appears to be the major cause of transmission, although the virus can also spread transplacentally and possibly through biting flies and infected semen or milk.
(4) Diagnostic plan and laboratory tests. Because enzootic lymphoma is the most common internal neoplasm in cattle, finding a tissue mass in one or more of the above organs is strongly suggestive of this disease.
(a) **Histopathology** can confirm the diagnosis.
(b) **Serologic** tests, most commonly the **AGID** test, can be used to confirm BLV infection, but it must be remembered that most infected animals do not develop clinical disease. False-positive tests can occur in calves due to colostral antibody, and **false-negative** tests can occur in recently infected cattle and in periparturient cows.
(5) Differential **diagnoses.** Approximately 10% of cattle with lymphoma have lymphoid leukemia, which can be differentiated from'persistent lymphocytosis by the presence of immature cells.
(6) Therapeutic plan. Treatment is rarely attempted.
(7) Prevention of disease through reduced exposure to contaminated body fluids (sanitation of instruments) is vital. Serologic tests can be used to identify infected cattle for removal from the herd.

2. Equine lymphosarcoma. There are four different forms of equine lymphoma, with each form characterized by the accumulation of abnormal lymphocytes in a different location.
a. Classifications and their clinical finding
(1) Multicentric or **generalized.** Multiple internal organs and lymph nodes are affected, causing depression, weight loss, and anorexia. This is the most commonly reported form of lymphosarcoma in mature horses, but it can occur in horses of any age.
(2) **Intestinal.** Masses are most common in the bowel wall and abdominal lymph nodes without peripheral lymphadenopathy. This is the most commonly reported form in juvenile or young adult horses. Affected horses develop generalized ill-thrift due to nutrient malabsorption and protein-losing enteropathy. Anemia and hypoalbuminemia are common.
(3) **Mediastinal** or thymic. Masses form in the cranial mediastinum and retropharyngeal lymph nodes, causing tachypnea, pleural effusions, and respiratory distress.
(4) **Cutaneous.** This may be the most common form of equine lymphoma, although it is not frequently reported. Affected horses develop multiple subcutaneous or dermal nodules of varying sizes. Spontaneous enlargement, regression, and regrowth are common. Nonaggressive forms can be present for years without morbidity, whereas aggressive forms lead to lymphadenopathy, internal metastasis, and death.
b. **Etiology.** There **does** not appear to be an infectious etiology.
c. **Diagnostic** plan and laboratory tests
(1) Biopsy. Diagnosis of any form of lymphoma is best made by histopathologic examination of a biopsy sample taken from a mass. Aspirates from masses are not as reliable. Masses can be found by external or rectal palpation or by thoracic radiographic examination.
(2) Abnormal lymphocytes also may be seen occasionally on examination of peripheral blood or thoracic or abdominal fluid.

(3) Clinical **pathology** abnormalities are usually nonspecific and reflect dehydration or organ damage caused by a tumor.
(4) **Hypercalcemia** and leukemia are each seen in less than *20%* of horses with lymphoma.
d. Therapeutic plan. Except for the nonaggressive form of cutaneous lymphoma, most horses die within 30 days of the onset of signs.
(1) Chemotherapeutic protocols similar to those used in people and dogs have been used to prolong the life of some horses.
(2) The **nonaggressive** cutaneous form can be treated with long-term **corticosteroids**, but recurrence is common if treatment is discontinued.

3. Plasma cell myeloma
a. Patient profile. Affected hones can be any age.
b. Clinical finding. Most affected animals exhibit some degree of weight loss and anorexia. Some animals have limb edema, bone pain, paresis, lymphadenopathy, and fever.
c. Etiology and **pathogenesis.** No etiologic agent has been identified. The malignant expansion of plasma cells leads to the infiltration of multiple organs, including bones and lymphoreticular organs. The secretion of immunoglobulin by neoplastic plasma cells frequently leads to monoclonal gammopathy.
d. **Diagnostic** plan and laboratory tests
(1) Protein electrophoresis to confirm monoclonal gammopathy is the best means of establishing an antemortem diagnosis.
(2) **Radiographic** examination of the bone may reveal multiple focal areas of bony lysis and periosteal reaction.
(3) Bone marrow and mass aspirates may reveal a homogeneous population of mononuclear tumor cells, some of which have nuclei with a "clock face" pattern. Normal aspirates may also be obtained from affected horses. **Immunofluorescent** stains can be used to label intracytoplasmic and surface immunoglobulin on these cells to confirm their identity.
(4) Clinical **pathology** abnormalities include anemia, hypoalburninemia, and hyperglobulinemia caused by monoclonal gammopathy. Proteinuria and a **hypocoagulable** state are also common.
e. Therapeutic plan. Most horses die within several months of the onset of signs. Chemotherapy can be attempted.

B. **Lymphadenitis** is the enlargement of lymphoid tissue due to inflammation. Lymphadenitis often is suppurative, leading to accumulations of purulent fluid (abscesses), which may be lanced or break open spontaneously for drainage. **Caseous** lymphadenitis is so named because abscesses frequently contain thick pus.

1. Patient profile. This disease primarily affects small ruminants.
2. Clinical finding. Infected animals usually develop caseous lymphadenitis within a few months of infection.
a. Goats usually develop abscesses in the superficial lymph nodes of the head and neck.
b. Sheep can develop similar lesions or peripheral abscesses but also commonly develop internal abscesses.
c. **Lesions**
(1) Animals with external lesions usually are bright and appetent, but the value of fleece and hide are decreased.
(2) Animals with internal abscesses usually are culled because of poor reproductive or production performance and chronic wasting disease.
3. **Etiology** and **pathogenesis**
a. **Etiology.** The disease is caused by Corynebacterium *pseudotuberculosis,* a short, curved, gram-positive rod.
b. **Pathogenesis.** C. pseudotuberculosis is usually introduced into a flock through an infected animal, which contaminates the environment and fomites with discharges from draining lesions. The organism may persist in the environment for

up to 6 months. Infection occurs when susceptible animals inhale or ingest the organism or when the organism gains entry through contact with damaged skin. Shearing instruments are particularly important in transmission.

4. Diagnostic plan and laboratory tests. Findings of internal or external suppurative lymphadenitis in small ruminants without evidence of another inflammatory focus is strongly suggestive of caseous lymphadenitis.
   a. Bacteriologic culture. The diagnosis can be confirmed by bacteriologic culture of pus.
   b. Serologic tests have been developed to identify infected animals, but the accuracy of these tests has not been established.

5. Therapeutic plan
   a. Isolation. Animals with signs of caseous lymphadenitis should be isolated from healthy animals. Animals may be returned to the flock when all of the lesions have healed, but these animals should be observed for recurrence of lesions. Healthy animals should not be allowed to contact equipment or facilities used for infected animals.
   b. Draining lesions should be lavaged with dilute antiseptic solutions. Thin-walled abscesses may also be lanced to facilitate drainage.
   c. Antibiotics are not thought to speed recovery.

6. Prevention
   a. Environmental hygiene. Facilities and shearing procedures should be checked to minimize skin trauma, and shearing blades should be sanitized between animals in diseased flocks.
   b. Vaccinations that appear to reduce severity of infection are available in Canada.
   c. Serologic tests and the removal of infected animals can be used to eradicate the disease from a flock.

IV. IMMUNE DEFICIENCY SYNDROMES

A. Immune deficiency syndromes of horses

1. Failure of passive transfer (FPT) is discussed in Chapter 18 IV.

2. Combined immune deficiency syndrome (CID)
   a. Patient profile. CID usually affects Arabian foals during the first few months of life as the maternal antibody wanes. As many as 25% of Arabian horses may be CID carriers.
   b. Clinical findings are associated with several diseases.
      (1) Infectious diseases. Chronic or recurrent pneumonia, enteritis, and sepsis are the most common infectious diseases associated with CID. These diseases can be caused by organisms not normally considered pathogenic.
      (2) Affected animals usually have persistent lymphopenia (less than 1000 cells/μL) and **hypoglobulinemia,** but CID also can be seen with other acute inflammatory conditions.
   c. Etiology and pathogenesis. CID is an autosomal recessive immunodeficiency of Arabian foals. The genetic defect has not been identified; affected animals appear to have a defect in stem cell maturation to both B and T cells.
   d. Diagnostic plan and laboratory tests. Because the parents of an affected foal are both carriers of the trait, care must be taken in establishing this diagnosis. Foals with CID have four characteristic findings:
      (1) Persistent lymphopenia
      (2) Absence of serum IgM either at birth before drinking colostrum or after 3 weeks of age (when the maternal antibody has been metabolized)
      (3) Absence of germinal centers and perivascular lymphoid sheaths in lymphoid tissue

      (4) Abnormal lymphocyte function assays, including failure to respond to intradermal phytohemagglutinin
   e. Therapeutic plan. Symptomatic treatment of infections can be attempted, but most foals with CID die before reaching the age of 6 months.
   f. Prevention. There is no test for CID carriers, except for the production of an affected foal.

3. Transient hypogammaglobulinemia
   a. Patient profile. Foals are most vulnerable in the first 3 months of life.
   b. Clinical findings. Chronic or recurrent infectious disorders are characteristic.
   c. Etiology and **pathogenesis.** There are few reports of this disorder, and it may often go unrecognized. When this disorder does occur, neonatal immunoglobulin synthesis does not begin early enough to replace metabolized colostral antibody. This immunodeficiency spontaneously resolves as the foal's antibody synthesis increases with time.
   d. Diagnostic plan and laboratory tests. Hypogammaglobulinemia with low concentrations of other classes of immunoglobulins is characteristic. Histopathologic examination of lymphoid tissue and lymphocyte function assays are normal.
   e. Therapeutic plan. Symptomatic treatment of the infections is indicated. Immunoglobulin synthesis increases with time, making foals less susceptible to repeated infections.

4. **Agammaglobulinemia**
   a. Patient profile. This disease has only been reported in male Thoroughbred and Standardbred foals.
   b. Clinical findings. Chronic and recurrent infections are common.
   c. Etiology. A suspected defect in B-cell maturation leads to an absence of B cells and antibody production. Cell-mediated immunity is normal. That the disease only seems to occur in male Thoroughbred and Standardbred foals suggests x-linked inheritance.
   d. Diagnostic plan and laboratory tests. Although affected horses have normal blood lymphocyte counts, labeling demonstrates a lack of B cells. All classes of immunoglobulin are absent or found in very low concentrations. Tests of T-cell function are normal.
   e. Therapeutic plan. Symptomatic treatment of infections may be attempted. Affected horses may live for several years, whereas most other hones with congenital immunodeficiencies die as foals.

5. Selective IgM deficiency
   a. Patient profile and history. Animals of any age may be affected, but cases often occur in one of three groups of horses:
      (1) Foals that show signs similar to CID and die in the first year of life
      (2) Juveniles that show signs similar to agammaglobulinemia and die before adulthood
      (3) Adult horses, many of which have or develop lymphoproliferative disorders
   b. Clinical findings. Affected horses show signs of poor growth and chronic or remittent infection.
   c. Etiology. The cause of the disease is unknown. Some forms may be hereditary, but this has not been determined.
   d. Diagnostic plan and laboratory tests. Affected horses have persistently low serum IgM concentrations, with normal to high concentrations of other immunoglobulins. In most affected horses, lymphocyte function tests and lymphoid tissue histopathology are normal. Older hones should be examined for lymphosarcoma.
   e. Therapeutic plan. Symptomatic treatment of infection can be attempted, but most affected animals die within 1 year.

B. Immune deficiency syndromes of ruminants

1. FPT is discussed in Chapter 18 IV.

2. Bovine leukocyte adhesion deficiency (BLAD)
   a. Clinical findings

(1) **Infections.** Affected calves, within the first months of life, develop chronic or recurrent bacterial infections. Oral infections, bronchopneumonia, enteritis, and dermatitis are the most common diseases.

(2) Clinical signs. Fever, lymphadenopathy, and very high (more than 40,000 cells/μL) peripheral blood neutrophil counts are commonly reported.

(3) Serum biochemical abnormalities are not specific to BLAD but include hypoalbuminernia, hyperglobulinemia, low serum creatinine, and electrolyte loss with diarrhea.

b. Etiology and pathogenesis. BLAD is an autosomal recessive immunodeficiency of Holstein calves. A point mutation in the CD18 gene leads to a defect in the Mac-1 surface glycoprotein, a β-2 integrin, causing impaired leukocyte adhesion and migration in homozygotes.

c. Diagnostic plan and laboratory tests. Young Holstein cattle with the mentioned clinical signs and laboratory abnormalities should be suspected as having BLAD. Additionally, histopathologic demonstration of the absence of neutrophilic infiltrates around bacterial foci is supportive. Definitive diagnosis can be made using a polymerase chain **reaction** test. This test identifies both heterozygous carriers and homozygotes.

d. Therapeutic plan. Most affected calves die within the first year of life. Antimicrobial drugs can be used to treat infections temporarily.

e. Prevention. Bulls used for stud should be tested as potential carriers. Efforts should be made to limit inbreeding.

3. **Chédiak-Higashi** syndrome

a. Clinical findings. Affected animals have a dilute coat color and complete or partial ocular albinism. They suffer from chronic or recurrent pulmonary and gastrointestinal infection and typically grow poorly.

b. Etiology and pathogenesis. Chédiak-Higashi syndrome is an autosomal recessive irnmunodeficiency of Hereford and Brangus calves. The defect leads to fusion and enlargement of granule-containing cells, including granulocytic leukocytes and melanocytes. This causes impaired immune function and abnormal coat color.

c. Diagnostic plan and laboratory tests. In addition to characteristic clinical features and abnormal tests of immune function, granulocytic leukocytes and melanocytes typically contain very large granules.

d. **Therapeutic** plan. Symptomatic treatment of infections is possible, but most affected animals die within 1 year.

4. Immunodeficiency induced by viral **or** bacterial **infections**

a. Clinical **findings.** Secondary immunodeficiency includes a broad spectrum of possible disease signs caused by the recrudescence of latent infections, as well as new infections. Clinical signs relate to the site and nature of the infection. Typically, secondary infections are recognized as the abrupt worsening in clinical condition. In some cases, the primary infection may be subclinical.

b. Etiology. Many infectious conditions cause secondary immunodeficiency by consuming or sequestering leukocytes, suppressing marrow production, or altering leukocvte function. Bovine viral diarrhea virus and sepsis are just two of many possible etiologies.

c. Diagnostic plan and laboratory tests. Bacteriologic and virologic culture techniques and serologic tests are used to identify both primary and secondary infectious agents.

d. Therapeutic plan. Treatment should be based on the nature and site of the secondary infection. If possible, the primary infection should also be treated.

STUDY QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the ONE numbered answer or completion that is BEST in each case.

1. Which one of the following neoplastic diseases has the best prognosis for long-term survival?

(1) Cutaneous lymphoma in a l-year-old calf
(2) Multicentric lymphoma in a 6-month-old calf
(3) Thymic lymphoma in a 9-month-old calf
(4) Multicentric lymphoma in a 5-year-old cow
(5) Cutaneous lymphoma in a 12-year-old horse

2. Which one of the following staternents regarding persistent lymphocytosis in cattle is true?

(1) It is seen in most cattle infected with the bovine *leukosis* virus (BLV).
(2) It is composed of normal lymphocytes.
(3) It is most common in cattle with lymphoma.
(4) It is synonymous with lymphoblastic leukemia.
(5) It is a characteristic finding in cattle with the leukocyte adhesion deficiency.

3. Which one of the following statements regarding equine viral arteritis (EVA) is true?

(1) Efforts to prevent the spread of disease should focus on insect control.
(2) Anemia occurs due to immune-mediated hemolysis.
(3) Clinical disease is characterized by high morbidity and mortality.
(4) Subclinical infections in stallions are the most common source of infection.
(5) Horses should be vaccinated against this disease in preparation for interstate or international transport.

4. Which statement regarding water intoxication in cattle is true? Water intoxication:

(1) causes anemia through Heinz body formation.
(2) causes neurologic signs due to the rapid movement of sodium out of the brain.
(3) causes intravascular hemolysis and hemoglobinuria.
(4) should be treated aggressively to rapidly normalize serum electrolyte concentrations.
(5) reduces sodium concentrations in the cerebrospinal fluid (CSF) below the plasma sodium concentration.

DIRECTIONS: Each of the numbered items or incomplete statements in this section is negatively phrased, as indicated by a capitalized word such as NOT, LEAST, or EXCEPT. Select the **ONE** numbered answer or completion that is BEST in each case.

5. **Infestation with** which **intracellular** parasite is **LEAST likely** to respond to treatment with *oxytetracycline?*

(1) *Anaplasma marginate*
(2) *Babesia* bigemina
(3) *Eperythrozoon suis*
(4) *Ehrlichia equi*
(5) *Eperythrozoon* wenyoni

6. **Which** one **of** the **following signs** is NOT typical of the **regenerative response** to anemia?

(1) **Basophilic** stippling in cattle
(2) Pofychromasia in cattle
(3) Macrocytosis in pigs
(4) Reticulocytosis in hones
(5) Marrow erythroid stem cell hyperplasia in horses

7. Which one of the following vector–pathogen associations is NOT correct!

(1) Biting flies—leptospirosis
(2) Biting flies—bovine leukosis virus (BLV)
(3) Ticks—anaplasmosis
(4) Biting flies—equine infectious anemia (EIA) virus
(5) Keds—eperythrozoonosis

8. An Arabian foal is suspected of having combined immune deficiency syndrome (CID). Which one of the following findings is NOT characteristic7

(1) Persistent lymphopenia
(2) Lymphadenopathy
(3) Abnormal lymphocyte function assays
(4) Absence of lymphoid germinal centers
(5) Low serum immunoglobulin M (IgM)

9. Several sheep in a flock are noted to have peripheral lymphadenopathy. Aspiration of an enlarged lymph node yields a thick white pus. Which one of the following statements is NOT an appropriate recommendation7

(1) Shearing equipment should be sanitized between sheep.
(2) Affected sheep should be isolated from the remainder of the flock.
(3) Sheep should be treated with a topical acaricide to eliminate keds.
(4) Facilities should be checked for hazards promoting skin trauma.
(5) Serologic testing could be performed to identify suspected carrier sheep.

10. A horse being treated with penicillin and phenylbutazone for respiratory infection develops mild anemia, peripheral edema, and petechiation of mucous membranes. Which choice would NOT be a logical course of action?

(1) Perform a Coggins test for equine infectious anemia (EIA).
(2) Perform a skin biopsy.
(3) Examine erythrocytes for autoagglutination.
(4) Discontinue penicillin administration.
(5) Vaccinate against Streptococcus *equi* infection.

11. Which one of the following morphological descriptions is NOT true?

(1) Babesia *equi*—Maltese cross in erythrocytes
(2) Anaplasma central—small bodies near the center of erythrocytes
(3) *Eperythrozoon* ovis—ring form in erythrocytes
(4) Anaplasma marginale--free organisms in plasma
(5) Ehrlichia *equi*—small bodies in neutrophils

12. A positive Coombs' test would NOT be likely for which one of the following causes of anemia in large animals7

(1) Neonatal isoerythrolysis
(2) Red maple toxicosis
(3) Penicillin-induced, immune-mediated hemolytic anemia
(4) Equine infectious anemia (EIA)
(5) Equine lymphosarcoma

ANSWERS AND EXPLANATIONS

1. The answer is **5** [III A 2 a (4)]. Cutaneous lymphoma in horses may exist in a nonaggressive form. Affected horses often live for years, while clinical signs wax and wane. In contrast, almost all cattle with lymphoma die within 30 days of the first apparent clinical signs. Spontaneous regression of cutaneous lymphoma in cattle has been reported, but affected animals frequently die of metastatic tumor masses within 6 months.

2. The answer is **2** [III A 1 b (1)]. Persistent lymphocytosis is composed of normal, nonneoplastic lymphocytes and is seen in a small subset (30%) of cattle infected with the bovine leukosis virus (BLV). It is an inconsistent finding in cattle with lymphoma. Persistent neutrophilia is the characteristic finding for cattle with the leukocyte adhesion deficiency.

3. The answer is **4** [II A 1 b (2), (4)]. Equine viral arteritis (EVA) is most commonly spread by aerosol or copulation with a carrier stallion. Insect transmission and immune-mediated hemolysis are characteristics of equine infectious anemia (EIA) but not viral arteritis. Viral arteritis is rarely fatal, and vaccination leads to antibody titers, which may preclude interstate or international transport.

4. The answer is 3 [I D 2 d (1) (a), (d)]. Water intoxication causes a rapid drop in plasma osmolality and osmotic intravascular hemolysis. Sodium concentration in the cerebrospinal fluid (CSF) is higher than that in the diluted plasma, leading to rapid movement of water into the brain, cerebral edema, and neurologic signs. Rapid administration of intravenous fluids can worsen clinical signs.

5. The answer is **2** [I D 2 a (2)]. Oxytetracycline is an effective antibiotic against rickettsial organisms of the genus Anaplasma, *Eperythrozoon,* and Ehrlichia but is not effective against the protozoon parasite ***Babesia bigemina***. Imidocarb is the most frequently used babesicidal drug.

6. The answer is **4** [I A 2 d (1)]. Horses do not get reticulocytosis. In other large animal species, reticulocytosis, macrocytosis, polychromasia, and basophilic stippling all are seen in the peripheral blood of animals with regenerative anemia. In horses, the detection of erythroid stem cell hyperplasia in the bone marrow is often the only way to determine if anemia is regenerative.

7. The answer is **1** [I D 2 a (4)]. Leptospirosis is caused by the ingestion or inhalation of organisms. Arthropod transmission is not thought to occur or to be of major importance. Bovine leukosis virus (BLV) is thought to be spread iatrogenically in many cases, but it can be isolated from biting flies. Arthropod transmission is thought to be the major route for Anaplasma, *Eperythrozoon,* and the equine infectious anemia (EIA) virus.

8. The answer is **2** [IV A 2 d]. Combined immunodeficiency syndrome (CID) is caused by a defect in lymphocyte maturation, which leads to lymphopenia, low immunoglobulin production, abnormal function tests, and absence of germinal centers. Lymphadenopathy is not seen.

9. The answer is 3 [III B 2, 5, 6]. The most likely diagnosis is caseous lymphadenitis. Efforts should be made to prevent the transmission of organisms to uninfected sheep and to decrease skin trauma. Identification and separation of infected sheep aids in the prevention of new cases. Arthropods are not thought to be important vectors.

10. The answer is *5* [II A 1 a, b]. Clinical signs are compatible with vasculitis (as seen with EIA or EVA), immune-mediated anemia and thrombocytopenia, or purpura hemorrhagica. Purpura hemorrhagica can be diagnosed by a skin biopsy and may be exacerbated by exposure to streptococcal antigens.

11. The answer is **4** [I D 2 a (3) (a), (b)]. Of the important intraerythrocytic parasites, only ***Eperythrozoon*** organisms are found free in the plasma.

12. The answer is **2** [I D 1 c (1) (e)]. A positive Coombs' test suggests that erythrocytes are coated with antibody, which occurs with immune-mediated hemolysis. Hemolysis with red maple toxicosis is caused by oxidative injury to erythrocytes and is not immune-mediated.